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THE TREATMENT OF MYOTONIA

BY

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A NUMBER of reports have appeared in the medical literature dealing with the symptomatic relief of dystrophia myotonica and myotonia congenita. Quinine has been used for many years, and is acknowledged to be of definite value in the relief of the myotonia in myotonia congenita, though less effective and often ineffective in dystrophia myotonica. More recently the dramatic evolution of the corticoids inevitably led to their application to these conditions, so that Shy and McEachern (1951) were able to report that corticotrophin reduced the duration of myotonia in one case of myotonia congenita and two of dystrophia myotonica, but that cortisone was less effective. Reese and Peters (1952) and Garai (1954) also reported that corticotrophin would shorten the myotonia and increase the power in cases of dystrophia myotonica. Cortisone was not used in these two series.

In none of these reports does there appear any objective recording either of muscle power or of the duration of myotonia, and experience leads one to the conclusion that the subjective impressions of patients suffering from dystrophia myotonica are liable to appreciable personal variations. We then evolved a simple and practical method of recording power and myotonia, as shown in the next section, and with its aid proceeded to assess the effects of the corticoids. During the period of the investigation Geschwind and Simpson (1955) published their findings on the beneficial effects of procaine amide using a similar though not identical recording technique. We accordingly carried out further experiments with procaine amide in addition to the corticoid group. It will be seen that with our material we were not able to confirm the results obtained by Geschwind and Simpson.

TECHNIQUE OF RECORDING

The correct assessment of the precise benefits of treatment in these conditions depends upon objective recording both of maximum power and

of the duration of myotonia. After some recordings had been made with concentric needle electrodes and an oscilloscopic electromyograph, it was discovered that the routine electroencephalographic apparatus could easily be adapted to provide an excellent myograph using surface electrodes. It is clear that this has practical advantages for the patient in whom serial recordings are required.

The muscles in which myotonia on voluntary action is most easily demonstrable are the flexors of the fingers. In order to record myotonia, therefore, two ordinary EEG surface electrodes were placed over the muscle bodies of the long flexors of the fingers, 2 cm. apart. Leads from these were taken into an Ediswan 8-channel EEG and the gains adjusted to give progressive amplification. The technique of increasing the gain on successive channels facilitates the identification of the end-point of myotonia. It is necessary to switch off the pens recording the higher gains during the period of voluntary action and in the first seconds of relaxation; the higher gains can then be reintroduced as the myotonic potentials are dying away (fig. 3). At a given signal the subject was asked to grip a dynamometer constructed from a sphygmomanometer cuff attached to a mercury monometer (*see* fig. 1). The pressure within this

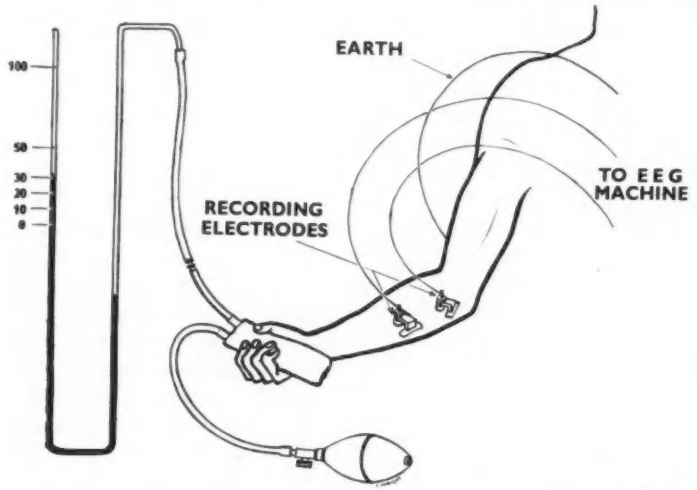

FIG. 1.—Apparatus for recording power and myotonia of flexores digitorum.

dynamometer bag could be adjusted to a statutory zero. The normal power of grip, maintained for 5 seconds, ranged from 100 to 140 mm. of mercury. At each test the subject held his maximum grip for 5 seconds and was then asked to relax and allow the fingers to return to the position of rest. Using this technique the duration of the action potentials from the

flexor group after the instruction to relax does not exceed a fraction of a second in the normal (fig. 2). In the myotonic, by contrast, these action

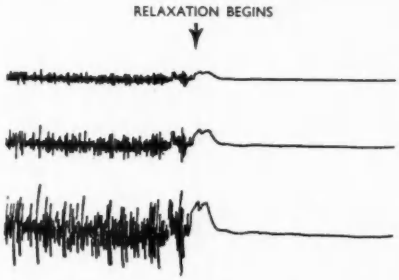

FIG. 2.—The normal record with this apparatus. Time scale 1 inch=1 second.

potentials continue for a variable time according to the severity of the myotonia, ranging in our cases from 4 to 19 seconds. At each test therefore three separate grips were recorded at an interval of 3 minutes between each in order to obviate the effect of "working off" on the second and third recordings. It will be noted that the end-point of the myotonic discharge as recorded by this method, particularly in those cases in whom the duration of the myotonia is prolonged, is not always absolutely clearcut, but can usually be placed to within 1 or 2 seconds.

"WORKING OFF"

It is well known that for a period of 1 to 2 seconds after a single contraction of a myotonic muscle, a subsequent contraction may be accompanied by myotonia of shorter duration. The effect of cumulative and a series of rapidly repeated contractions may almost abolish the myotonia for a time. This phenomenon may be found both in myotonia congenita and in dystrophia myotonica. In most cases it is only the myotonia which is altered and there is little or no effect on the power. In Case 11 of this series (myotonia congenita) however, the process of working off resulted in a considerable increase in power, a phenomenon we have also observed in another case of myotonia congenita (fig. 6). From the technical viewpoint this working-off effect must be avoided if satisfactory evaluation of treatment is to be made.

EFFECT OF TEMPERATURE

In making these records due attention was paid to the temperature conditions. In earlier experiments we were able to show that reduction in temperature prolonged the duration of myotonia considerably; recordings from one patient in whom the skin temperature on the forearm was reduced from 31° C. to 25° C. by cooling in a water bath, indicated

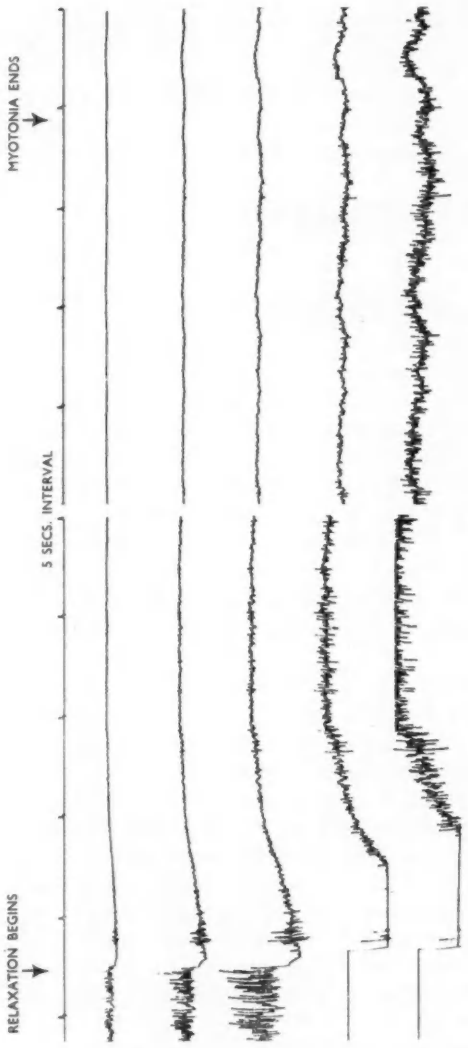

FIG. 3.—Record of relaxation in Case 5. Skin temperature over the muscle 31° C. Duration of myotonia is 13 seconds (time in seconds).

that the myotonia was prolonged from 17 to 32 seconds (figs. 3 and 4). Elevation of the skin temperature from 31° to 33° C. had no effect on the duration of myotonia. Thus we considered that maintenance of the skin temperature at or above 30° C. would eliminate errors due to temperature variation.

Geschwind and Simpson (1955) who published their report towards the

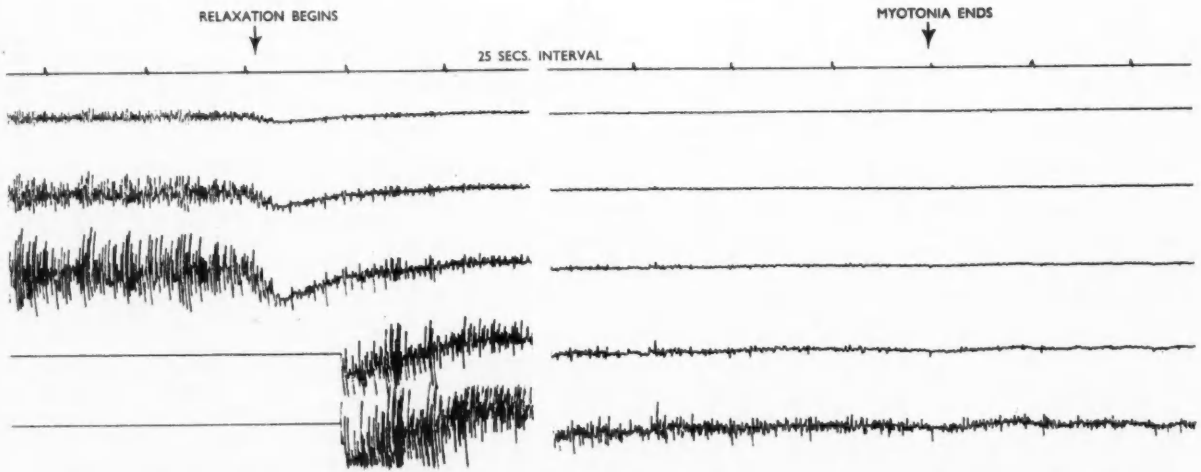

FIG. 4.—The same after cooling. Skin temperature 25° C. Duration of myotonia is 32 seconds (time in seconds).

conclusion of our investigation, discussed the implication of isometric and isotonic contraction. Our view, however, is that maximum voluntary effort is required to bring out the true myotonic effect. The dynamometer readings are therefore of considerable importance in the assessment of myotonia, since maximum power should be exerted and recorded on all occasions in order to obtain comparable readings of myotonia. This is not possible in either strictly isotonic or isometric contraction.

Clinical Material

Summaries of the individual cases and accounts of the separate results appear at the end of the paper. The treated group comprised 10 cases of dystrophia myotonica and 1 case of myotonia congenita (Case 11). The duration of symptoms in the former ranged from 2 to 14 years, whilst the last patient, now aged 50, recalled that he had been affected from the age of 4. Their ages ranged from 22 to 50. In 4 patients myotonia was the leading symptom, in 3 weakness partly overshadowed the myotonia, while in the remaining 4, myotonia and weakness appeared as equal handicaps. Table I sets out the principal clinical features of the group.

Table I

Case No.	*Sex*	*Age*	*Duration of disease*	*Principal symptom*		*Power of grip*	*Duration of myotonia*	*Family history*	*Keto-steroid excretion*
			years	*Myotonia*	*Weakness*	mm.Hg	seconds		mg./24 hours
1	M	28	6	x	x	45	6	Yes	5·7
2	M	37	12	x	x	70	17	No	7·5
3	M	28	6		x	35	6	Yes	4·4
4	M	44	14		x	20	4	Yes	–
5	M	29	12	x		105	15	No	4·8
6	M	22	5	x		60	19	Yes	3·5
7	F	48	2	x	x	55	5	Yes	1·5
8	M	48	10	x	x	45	15	Yes	6·2
9	M	49	4	x	x	40	4	Yes	–
10	M	22	6	x		55	10	No	4·0
11	M	50	46	x		50–100	12	No	10·8

It will be noted that in cases 3, 4 and 9 in whom weakness was the preponderant symptom, the duration of myotonia was only 4, 6 and 4 seconds respectively, although the average for the group was 10·3 seconds. The power of grip in these cases measured 35, 20 and 40 mm.Hg, against an average of 52·7 mm.Hg. In the predominantly myotonic group, which included the case of myotonia congenita, the myotonia lasted from 10 to 19 seconds, and the power ranged from 55 to 105 mm.Hg. These points have a bearing on the results of treatment and will be discussed later. All patients were observed as in-patients in the first instance, and

TABLE II

Case No.	*Corticotrophin*	*Cortisone*	*D.O.C.A.*	*Procaine amide*	*KCl*
1			x		x
2	x	x		x	
3		x	x		
4			x		
5		x		x	
6	x	x			
7	x	x	x	x	x
8		x		x	
9	x		x		x
10		x			x
11	x	x		x	
	5	8	5	5	4

treatment was begun during this period. Table II summarizes the treatment given: corticotrophin was given to 5, cortisone to 8, desoxycorticosterone acetate (D.O.C.A.) to 5, procaine amide to 5 and potassium chloride to 4 patients.

RESULTS OF TREATMENT

Corticotrophin.—Five patients were treated with corticotrophin and each received 20 units of the gel intra-muscularly twice daily. Two (Nos. 2 and 6) in whom the myotonia was particularly severe, responded very well. There was a latent period of some seven days in the case of both corticotrophin and cortisone. The duration of myotonia was reduced by 75 per cent and 55 per cent in these 2 cases, and six days after the cessation of treatment had returned to its original severity (fig. 5).

Case 11, myotonia congenita, exhibited a similar therapeutic response. We had begun to treat him before evolving the electromyographic system of recording, and with corticotrophin gel 25 units twice weekly he experienced an excellent subjective and objective response as judged by ordinary clinical means. The treatment was discontinued and at the end of a week his recorded myotonia extended to 12 seconds. Corticotrophin gel 25 units three times weekly was recommenced with subsequent reduction of the myotonia to under 2 seconds. The improvement was subsequently maintained with cortisone (fig. 6).

Patients 7 and 9 had myotonia of only 5 seconds' duration which corticotrophin reduced to 2·5 seconds.

Cortisone.—Eight patients were treated with cortisone, either in a course of 100 mg. daily for ten days or as maintenance treatment in a dose of 25 to 75 mg. daily. Three of the patients (5, 8 and 10) had severe myotonia and their myotonic duration was reduced by over 50 per cent at the end of the seven-day latent period (fig. 7). In Case 8 voluntary myotonia was almost completely abolished (figs. 8 and 9) as was mechanical

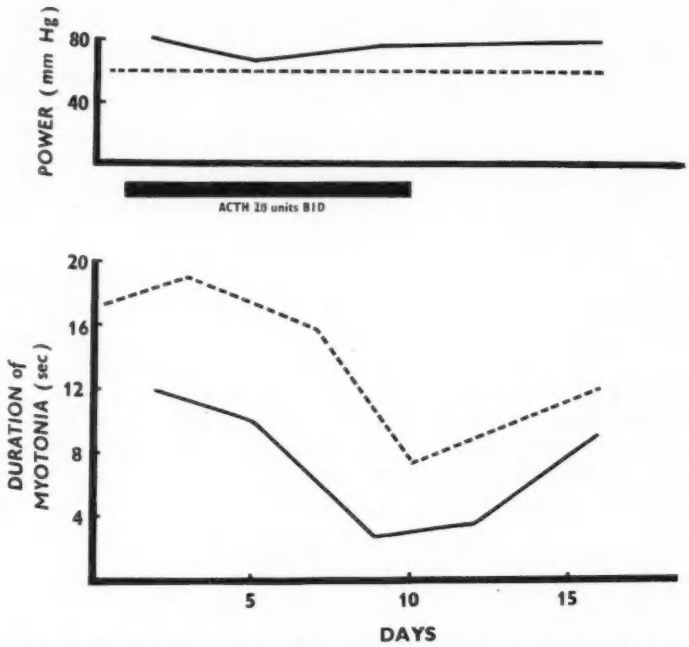

FIG. 5.—The effect of corticotrophin on power and duration of myotonia in dystrophia myotonica.

———— Case 2. – – – – – – – Case 6.

The myotonia is reduced. Power is unchanged.

myotonia. The first 2 were continued on a maintenance dose, while the third relapsed after the cessation of treatment. Patient 7 was treated similarly but the myotonic duration was shorter and the result correspondingly less striking, though the subjective improvement warranted the continuation of the drug. Patients 6 and 11 were maintained on cortisone after an initial course of corticotrophin. Only patient 3, whose myotonia was of 6 seconds' duration, failed to show any definite improvement.

It will be noted that the improvement is exclusively in the duration of the myotonia. Neither cortisone nor corticotrophin produced any significant change in power as measured by the dynamometer. Even in Case 11, where maximum power only occurred after working off, virtual abolition of the myotonia by cortisone did not increase his initial power (fig. 6).

Desoxycorticosterone acetate.—D.O.C.A. was given to 5 patients in a dosage of 5 to 10 mg. intramuscularly twice daily. In Cases 7 and 9, the treatment was discontinued after five days because of general symptoms

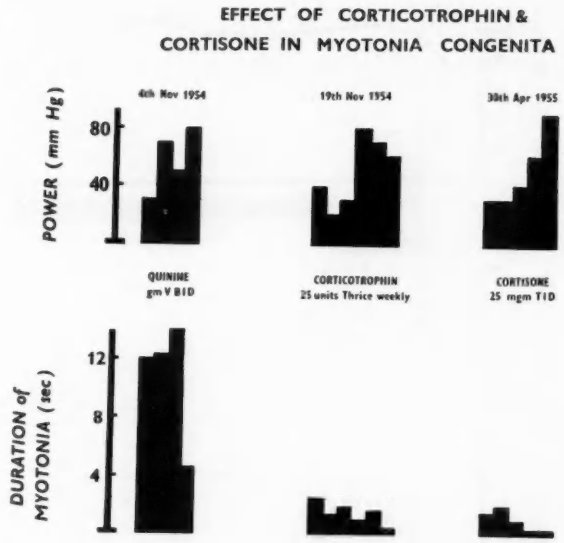

FIG. 6 (*Case 11*).—The vertical columns in the three groups represent voluntary contractions separated by 30-second intervals. The working-off effect results in increase in power and reduction of myotonia. The effect of corticotrophin and cortisone is shown in the second and third groups. Myotonia is greatly reduced. Basic power is not affected. The working-off phenomenon is still present.

of malaise with overt œdema. In the 3 remaining cases the course was continued for eight to ten days. In no case was there any reduction in myotonic duration or increase in power. In Case 1 the serum potassium fell during treatment from 4·8 to 3·6 meq./litre on the eighth day without any effect on the myotonia, whilst in Case 3 the myotonic duration was actually doubled.

Procaine amide.—Following the suggestion of Geschwind and Simpson (1955) we added procaine amide to the series. Five patients received from 1·0 to 2·0 grammes daily in divided doses. Two (Cases 7 and 11) complained of vomiting, insomnia, pains in the limbs and depression, so that the full course could not be completed. Patient 2 was treated for a fortnight with a 30 per cent reduction in an initial myotonia of 17 seconds. Patients 5 and 8 showed neither reduction in myotonia nor increase in power after seven days of treatment (fig. 7). Indeed, in patient 8 the myotonia was actually prolonged. It may be mentioned that the last 3 cases responded well to subsequent treatment with cortisone. It may well be that the difference between our results and those of Geschwind and Simpson is explained by the fact that they used larger doses of procaine amide, ranging from 2 grammes to 5 grammes daily.

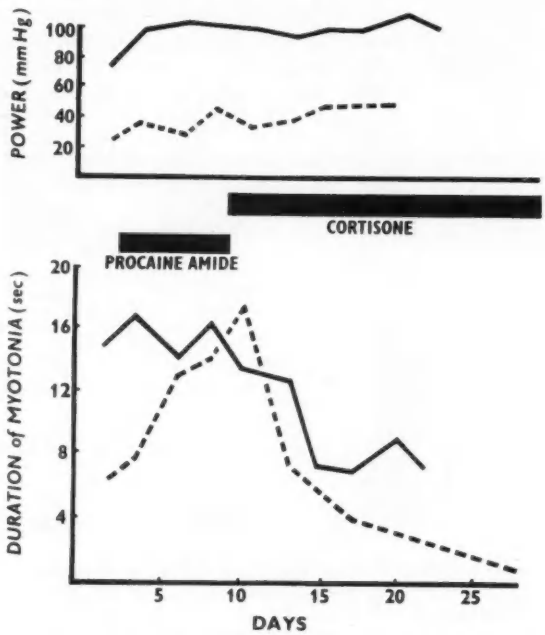

FIG. 7.—The effect of procaine amide and cortisone on power and duration of myotonia in dystrophia myotonica.
———— Case 5. – – – – – – – Case 8.
The myotonia is increased or unaffected by procaine amide, but cortisone produces definite reduction.

Quinine.—No direct assessment of the action of quinine was made. However, 3 of the patients had taken quinine by mouth prior to their initial course of cortisone or corticotrophin. Patients 2 and 11 noted definite though slight improvement; the former in diminishing myotonia of the masseters, the latter in the myotonia of the orbicularis oculi. Patient 5 reported no effect at all. All 3 felt that the subsequent effect of the corticoids was much greater.

The combined results of treatment with cortisone, corticotrophin, D.O.C.A., and procaine amide are illustrated in fig. 10 (A and B).

DISCUSSION

Practical considerations.—Patients in the myotonic group may exhibit one or both of the principal symptoms of myotonia and dystrophic weakness. In myotonia congenita the myotonic feature is manifestly preponderant although the muscle power in our cases (not included in this survey) has not been so great as the muscular development might

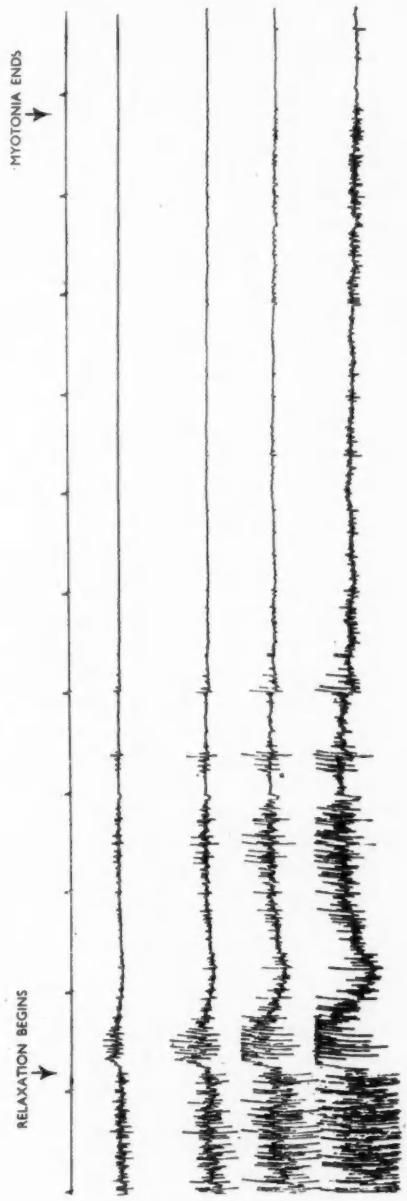

FIG. 8.—Record of duration of myotonia in Case 8 during treatment with procaine amide (9–10 seconds).

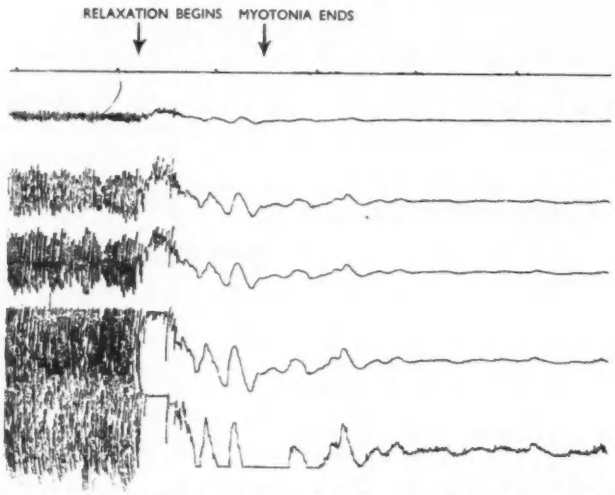

FIG. 9.—Record of the same case on twentieth day of cortisone treatment (myotonia under 2 seconds).

suggest. The cases of dystrophia myotonica tend to fall into two functional groups according to the relative prominence of each of the two symptoms.

The prolonged administration of corticoids is attended by very definite hazards, and it is important, therefore, to balance practical benefit against the disadvantages of the therapy. It is clear that in order to produce lasting improvement in the myotonic diathesis treatment must be given consistently, for a short course produces only temporary benefit. On the basis of our experience with this group of patients, we feel justified in concluding that corticoid therapy is likely to be of real value only to those patients who find moderate to severe myotonia (over 5 seconds) their principal handicap, and in whom the dystrophic element is playing a minor role. The first step in management, therefore, is to assess the duration of the myotonia. If it is prolonged beyond 5 seconds, a course of treatment should be given for fourteen to twenty-one days. By the end of this time it will be possible to decide whether real functional benefit results from the diminution in myotonia. If improvement is satisfactory. corticoid therapy should be continued at the minimum dose which is effective with the addition of quinine 5 grains t.i.d. by mouth. We feel it better to aim at moderate reduction in myotonia rather than risk infection or serious metabolic upset by giving unduly high dosage. Unlike Shy and McEachern (1951) we have not found corticotrophin more effective than cortisone, and the ease of administration of the latter makes it the more suitable for continuous treatment. Satisfactory maintenance dosage appears to be from 50 to 75 mg. daily. Two of our patients have already been receiving

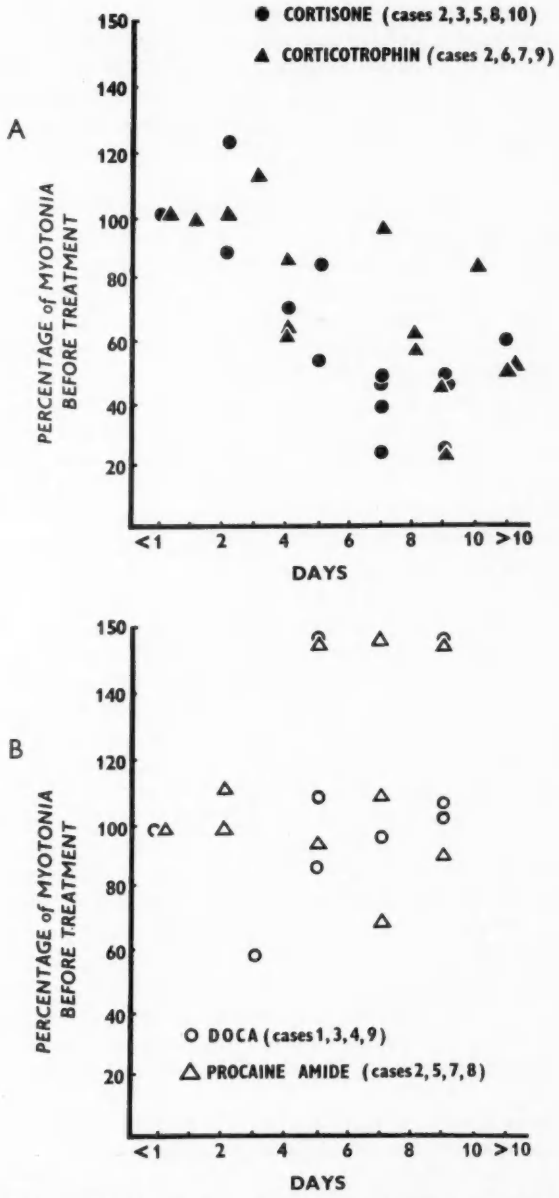

FIG. 10.—The combined results of treatment. Each point represents the mean of three readings. A, Cortisone and corticotrophin. B, D.O.C.A. and procaine amide. The scatter with cortisone and corticotrophin shows a downward trend. D.O.C.A. and procaine amide have no effect.

this for over nine months without adverse effects and with excellent symptomatic response. Other patients have been receiving cortisone for periods of from four to seven months. It is possible that patients with dystrophia myotonica and associated testicular dysfunction may develop osteoporosis as a result of prolonged corticoid therapy. A priori reasoning, therefore, suggests that concomitant treatment with androgens may be advisable.

Theoretical considerations.—The theoretical implications of these results appear to fall into two sections. The first comprises those relating to the ætiology of the disease, and the second those relating to the mechanism of production of the myotonia and to the related physiology of muscle action. The genetic background both to myotonia congenita and dystrophia myotonica is clearly established, but considerable doubts still exist as to the primary nature of the disorder in the individual. Despite the cogent pleading of Maas, we feel that sufficient clinical differences exist between myotonia congenita and dystrophia myotonica to warrant nosological differentiation between the two conditions. One cannot but be struck by the contrast between the pleomorphic picture of dystrophia myotonica with its widespread mesodermal, ectodermal and entodermal involvement and the monomorphic myotonic symptom of myotonia congenita. It may be that myotonia congenita represents a partial projection, a forme fruste as it were, of the full dystrophic picture (in much the same way that simple areflexia may occur in families in which the full picture of Friedreich's ataxia at times evolves). If this is so, one is justified in accepting the essential identity of the myotonic element in the two conditions. Structural changes in the muscles and other tissues would then depend on additional defects which may be referable, as suggested by Jager (1951) to an inherent pituitary disorder not seen in myotonia congenita. This notion is not of primary concern to us now, but it is interesting to note that all our dystrophic cases exhibited a very low ketosteroid excretion, whilst the figure in Case 11, the myotonia congenita, though on the low side, was much the highest in the group.

One cannot say whether continuous cortisone treatment will retain its initial efficacy. So far we have seen no sign of its potency waning. One wonders also if treatment will have any influence on the ultimate progress of the disorder, even though it cannot reverse the dystrophic element. It is at least conceivable that the fundamental process may be susceptible to corticoids and that, if they can be given sufficiently early in the development of dystrophia myotonica, the dystrophic process may be slowed if not arrested.

The results which we have recorded make it possible to advance further views upon the phenomenon of myotonia. After some early disputation it is now established that the disorder is localized to the muscle tissues themselves at a point distal to the motor end-plate. It seems probable

that once the depolarization of the muscle fibre membrane has taken place in the myotonic muscle there is established a locally regenerative circuit which continues to activate the contraction of the myofibrils. Normally such continued activation is only brought about by repetitive neural stimuli, and the discontinuance of nerve impulses is immediately followed by discontinuance of muscle contraction. Brown and Harvey (1939) have shown that myotonic goat muscle is exceedingly susceptible to the influence of potassium ions introduced intra-arterially. It may well be, therefore, that cortisone and corticotrophin modify the susceptibility of the muscle cell membrane to potassium ions, and in the same way the process of "working off" may also modify temporarily the ionic relationships of the cell membrane. It might be argued that cortisone works by actual elimination of potassium, but the inefficacy of D.O.C.A. particularly in the patient whose serum potassium was reduced to 3·6 m.eq./litre suggests that this is not so; neither does working off seem to act through a humoral factor since it takes place equally well when the local circulation is occluded. We are at the moment engaged upon a study of the effects of intra-arterial potassium chloride on normal and on treated and untreated myotonic muscle.

One final point. Denny-Brown and Nevin (1941) were led to believe that the phenomenon of myotonia following strong willed movement comprised not only a peripheral myotonic component but also a reflex central after-spasm. The almost total abolition of myotonia by cortisone does not suggest that there is this dual nature. The cramp-like contraction in palmaris longus and flexor carpi ulnaris noted by Denny-Brown and Nevin during relaxation of the grip is due, we think, to the synergistic action of these muscles when extensor digitorum is the agonist. This complication was avoided in our experiments by instructing the patients to allow the hand to relax without extending the fingers actively.

Case Reports

Case 1.—History.—A warehouseman, aged 28, was noted by his mother at the age of 10 to become thinner in the arms and legs. At 22 he developed difficulty in relaxing his grip. At 24 he suffered from the symptoms of a duodenal ulcer. His father had early baldness and cataract. On examination he was generally thin with weak musculature and myopathic facies. Myotonia was moderate, hair normal, testicular atrophy marked. Investigation showed early lens changes (slit-lamp); gonadotrophin excretion 5 M.U./twenty-four hours; 17-ketosteroids 5·7 mg./twenty-four hours.

Treatment.—He was given D.O.C.A. 10 mg. twice daily for eight days without effect, although the serum potassium was reduced from 4·8 to 3·6 m.eq./litre. Potassium chloride 1 gramme four-hourly was given, but had to be stopped on account of nausea after one day. Cortisone was not given because of the ulcer and the relatively mild myotonia.

Case 2.—History.—A clerk, aged 37, first experienced difficulty in relaxing the grip and the clenched teeth at the age of 29. At 32 he developed progressive foot-drop and later weakness of the arms. No family history was elicited. Examination revealed

frontal baldness, myopathic facies, bilateral foot-drop and weakness of the shoulder girdle muscles and left hand. Myotonia was severe but weakness the greater disability. Investigation showed early lens changes; creatine excretion 110 mg./twenty-four hours; gonadotrophin normal and 17-ketosteroids 7·5 mg./twenty-four hours.

Treatment.—He was treated first with corticotrophin for ten days (fig. 5) and showed marked relief of the myotonia, though the foot-drop was unaltered. The myotonia was reduced from 12 seconds to 3 seconds by the eighth day, and reverted to 10 seconds again six days after treatment ceased. The power of grip was unchanged. Later as an out-patient he was given procaine amide 0·5 gramme four times daily for seven days; there was no symptomatic relief, but myotonia was slightly reduced from 17 seconds to 11 seconds. Cortisone 75 mg. daily was then given, and though the duration of myotonia was reduced to between 2½ and 5 seconds he stressed that the weakness of the legs was not relieved. He has been fitted with foot springs and the cortisone was discontinued.

Case 3.—History.—An unemployed labourer, aged 28. At age 22 he began to drag the left foot, and a year later noticed weakness of the right hand. The weakness progressed and he also developed a tendency for the jaw to lock. His mother had cataract, 5 siblings were not affected. Examination showed frontal baldness, testicular atrophy, myopathic facies and severe generalized muscular weakness and wasting with moderate myotonia. The tendon reflexes were absent. Investigations revealed no lens changes; 17-ketosteroid excretion 4·4 mg./twenty-four hours.

Treatment was started with D.O.C.A. 10 mg. twice daily, and on the tenth day the duration of myotonia was somewhat prolonged. Cortisone 100 mg. daily was then begun, and on the seventh day of this treatment the myotonia had returned to its initial duration. Unfortunately the patient left hospital and treatment with cortisone could not be continued.

Case 4.—History.—An unemployed man, aged 44, had suffered from progressive weakness of the hands and later of the legs, beginning at age 30. He had not himself noticed any myotonia. His sister and one son aged 17 have dystrophia myotonica. Examination showed a thin man with severe generalized wasting and weakness. The sternomastoids were almost absent. Tendon reflexes were absent; frontal baldness, testicular atrophy and lenticular opacities were noted, and myotonia was relatively slight.

Treatment.—He was given injections of D.O.C.A. 10 mg. twice daily for ten days without any change either in power of grip or duration of myotonia.

Case 5.—History.—A coalminer, aged 29, first noticed delayed relaxation of grip at the age of 17, and this progressed to involve all muscle groups until he had to give up his job six months prior to examination. His wife had commented on his mournful expression and drooping head. No relevant family history obtained. Examination showed a well-built man with weakness of the facial muscles and sternomastoids but otherwise very good muscular power. Myotonia was very severe. Tendon reflexes sluggish. No baldness, testicular atrophy or lens opacities on slit-lamp examination. 17-ketosteroid excretion was 4·8 mg./twenty-four hours.

Treatment was commenced with procaine amide 0·25 gramme six-hourly, increased after three days to 0·5 gramme six-hourly. On the seventh day of treatment there was no subjective or objective change in power or myotonia. Cortisone 100 mg. daily was then substituted, and the duration of myotonia fell from between 14 and 17 seconds to 7 seconds on the seventh day of treatment. Increasing the dose of cortisone to 150 mg. produced no further effect. He was discharged on a maintenance dose of 75 mg. cortisone daily, but after two weeks the myotonia returned to its former duration. The dose is being increased.

Case 6.—History.—A labourer, aged 22, first noticed myotonia at the age of 16, but did not complain of weakness. His father has bilateral cataracts, and three members of the family hæmophilia. Examination showed generally slender musculature but no localized wasting; tendon reflexes depressed, myotonia severe. There was some testicular atrophy, but no baldness, or lenticular opacities on slit-lamp examination. 17-ketosteroid excretion was 3·5 mg./twenty-four hours. After the course of corticotrophin this increased to 8·5 mg./twenty-four hours.

Treatment was commenced with corticotrophin gel 20 units twice daily for ten days. There was good subjective relief and myotonia was reduced from nearly 20 seconds to between 7 and 8½ seconds on the ninth day, and had reverted to its initial duration by the nineteenth day. He was given cortisone 25 mg. daily as an out-patient which produced a slight amelioration, the dose being then increased to 50 mg. daily with good results. The myotonic duration is still 8 seconds, and he has been able to return to work.

Case 7.—History.—A housewife, aged 48, began to have weakness of the legs at the age of 46, having noticed myotonia some six months earlier. Her mother and one nephew had cataracts in early youth, her sister died at the age of 52 with dystrophia myotonica, and her daughter showed a slight myopathic facies without demonstrable myotonia. Examination revealed myopathic facies, hoarse voice, atrophic skin on the face, some generalized weakness with foot-drop and moderate myotonia. Tendon reflexes depressed. Slit-lamp examination showed lenticular opacities. 17-ketosteroid excretion 1·5 mg./twenty-four hours; gonadotrophins 6 M.U./twenty-four hours. The serum electrolytes were constant throughout treatment.

Treatment.—Corticotrophin 20 units twice daily was first given for fourteen days with reduction of myotonia from 5 to 2 seconds. After a week's interval, cortisone 100 mg. daily was started and the myotonia again reduced to between 1 and 2 seconds. D.O.C.A. 5 mg. twice daily was then substituted and the myotonia returned to its initial figure, accompanied by malaise and increased muscular weakness. She was discharged on cortisone 25 mg. daily and showed good subjective improvement, the myotonia remaining below 2 seconds. Later procaine amide 2 grammes daily was substituted for one week and the myotonia was prolonged to between 5 and 7 seconds again. She has now been having cortisone for eight months and is able to do her full household duties.

Case 8.—History.—A pattern inspector, aged 48, had had some locking of the jaw possibly since childhood. At the age of 38 his walking became slower and in the last four years there was more definite weakness of the legs. Of 4 siblings 2 brothers have similar symptoms. Examination showed a well-built man with frontal baldness, myopathic facies; slit-lamp examination showed no lenticular opacities. 17-ketosteroid excretion 6·2 mg./twenty-four hours.

Treatment was commenced with procaine amide 2 grammes daily, but over a period of seven days the duration of myotonia actually increased. We felt this was due to better co-operation from the patient in that he was now gripping considerably harder. Cortisone 100 mg. daily was then substituted, and on the eighth day of this treatment myotonia was reduced from between 15 and 19 seconds to 4 seconds. He was then discharged on a maintenance dose of 75 mg. daily, and eleven days later the myotonia registered less than 1 second. Power was possibly slightly increased. Mechanical myotonia and *langue en trefle* could no longer be elicited. His symptomatic improvement was striking, and he could now rise quickly from a low chair in which he had been sitting for fifteen minutes, whereas it took him several minutes to do this previously. Foot springs on a waist band have been fitted to correct the foot-drop.

Case 9.—History.—A plasterer, aged 49, first noticed weakness of the legs at the age of 46. Within eighteen months he had to give up work because of progressive

weakness. At the age of 44 he had a cataract removed from the right eye. He had also suffered from chronic bronchitis for many years. One sister had early cataract. Examination revealed frontal baldness, severe generalized weakness and wasting, absent tendon reflexes and relatively slight myotonia. There was cataract in the left eye, and testicular atrophy. Urinary gonadotrophin 6 M.U./twenty-four hours.

Treatment.—The administration of corticotrophin was followed by a slight decrease in duration of myotonia from 4 seconds to 2½ seconds. Potassium chloride 12 grammes daily was then added for two days and the improvement was maintained. The patient himself, however, was not impressed by any subjective relief of symptoms. D.O.C.A. 5 mg. twice daily was then given, and the myotonia reverted to its initial duration.

Case 10.—History.—A messenger boy, aged 22, first noticed myotonia of the hands and jaw at the age of 16. He did not complain of weakness. In the past three and a half years he had had a number of epileptic fits. No relevant family history was elicited. Examination revealed a myopathic facies, generally slender musculature with particular wasting of the sternomastoids. The testes were atrophic but hair and eyes normal. Gonadotrophin excretion was less than 7 M.U./twenty-four hours, and 17-ketosteroids 4 mg./twenty-four hours.

Treatment.—He was treated with cortisone 100 mg. daily, and myotonia was reduced from 8 to 3 seconds by the eighth day of treatment. Potassium chloride 2 grammes daily was then added and the reduction in myotonia persisted. By the eighth day after cessation of all treatment the duration again reached 10 seconds.

Case 11.—History.—A sheet metal worker, aged 50, had suffered from myotonia since his earliest childhood. He was unable to get on or off a bus and he would fall like a log if pushed unexpectedly. No history of similar affection in other members of the family could be elicited. Examination revealed good muscular development, severe myotonia but no weakness apart from slight wasting of the sternomastoids. There was no testicular atrophy or lenticular opacity. 17-ketosteroid excretion 10·8 mg. per twenty-four hours. The myotonia was readily worked off, and in addition, unlike the other cases investigated, full power was not exerted until the myotonia had been worked off.

Treatment.—He had been taking quinine 10 grammes daily for many years, which relieved the myotonia of orbicularis oculi, but not of other muscles. Treatment with corticotrophin 20 units twice daily for ten days appeared to abolish the myotonia completely, but objective recordings were not obtained; however, he was able to run up a flight of stairs whereas he could only mount two steps before. In view of this good result, injections of corticotrophin 25 units first twice then three times weekly were continued as an out-patient and the duration of myotonia varied from 14 seconds when no injection had been given for a week, to 2½ seconds when regular thrice-weekly injections were given. Treatment was changed in March 1955 to cortisone 75 mg. daily, and myotonia was virtually unrecordable in the hands though still troublesome in the legs. There was considerable symptomatic relief. Procaine amide was substituted for the cortisone in July 1955, but after three days he had to discontinue it because of severe pain in the legs. Four days later subjective myotonia was greater, and a duration of 5 to 6 seconds was recorded. He has now been on maintenance therapy with cortisone and corticotrophin for a total of one year.

SUMMARY

Ten cases of dystrophia and one case of myotonia congenita were treated with the following substances: cortisone, corticotrophin desoxycorticosterone acetate and procaine amide.

A quantitative method was devised for measuring the power of the grip, and the duration of the myotonia in the flexor digitorum sublimis.

Cortisone and corticotrophin reduced significantly the duration of myotonia in 8 out of 9 patients treated. In 3 of these cases the myotonia was virtually abolished. The muscle power was not affected. D.O.C.A. and procaine amide in the dosage used by us were without demonstrable effect on either power or myotonia. Quinine appeared to be less effective than cortisone or corticotrophin.

Treatment with cortisone is indicated only in those cases in which myotonia is the predominant symptom.

Some theoretical implications of the action of corticoids on myotonia are discussed. The effect may help to elucidate the mechanism of myotonia and other problems of muscle contraction.

We are indebted to Dr. F. R. Ferguson and to Dr. G. E. Smyth for permission to study their patients and to Mrs V. Emery for her help in recording the duration of myotonia.

REFERENCES

BROWN, G. L., and HARVEY, A. M. (1939) *Brain*, **62**, 341.
DENNY-BROWN, D., and NEVIN, S. (1941), *Brain*, **64**, 1.
GARAI, O. (1954) *J. Neurol. Neurosurg. Psychiat.*, **17**, 83.
GESCHWIND, N., and SIMPSON, J. A. (1955) *Brain*, **78**, 81.
DEN HARTOG JAGER, W. A. (1951) *Arch. Neurol. Psychiat., Chicago*, **66**, 178.
REESE, H. H., and PETERS, H. A. (1952) *Dis. nerv. Syst.*, **13**, 99.
SHY, G. M., and MCEACHERN, D. (1951) *Brain*, **74**, 354.

THE ENTORHINAL AREA; BEHAVIOURAL, EVOKED POTENTIAL, AND HISTOLOGICAL STUDIES OF ITS INTERRELATIONSHIPS WITH BRAIN-STEM REGIONS

BY

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IT has long been recognized that bilateral removal of the temporal lobes, including the hippocampus, amygdala and other structures grouped under the term "rhinencephalon," results in profound modification of behaviour (Klüver and Bucy, 1939). Such an ablation in the monkey is followed by extreme tameness, hypersexuality, an insatiable curiosity coupled with a "psychic blindness" or lack of appreciation of the significance of objects examined and a lack of normal social behaviour. Foci of abnormal activity in the temporal lobe in man are associated with aggressiveness and fits of rage.

More limited resections of portions of the temporal lobe have shed light on the possible significance of its different parts in behaviour mechanisms, although there is some lack of agreement about the results to be expected from such limited ablations, and it is generally conceded that limited removals do not result in the profound changes that follow total bilateral temporal lobectomy. Thus the early work of Bard and Mountcastle (1948) suggested that simple amygdalotomy in the cat was followed by most aggressive and vicious reactions to normally pleasurable stimuli, whereas a similar resection in the rat was followed by tameness. More extensive observations (Schreiner and Kling, 1953) have shown that while vicious behaviour does follow amygdalotomy in some cats, the majority are tamed and also show the hypersexuality noted by Klüver and Bucy in the monkey after a complete bilateral temporal lobectomy.

A different approach to the problem by the use of implanted recording electrodes in the hippocampus in chronic animal preparations (Green and Arduini, 1954) has clarified the interrelationships between the electrical activity of the hippocampus and the cerebral cortex. The desynchronization of the cortical electrical activity characteristic of arousal is accompanied by a rhythmic slow-wave discharge at 2–5 per second in the hippocampus, whereas a resting animal with an alpha cortical rhythm shows desyn-

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chronized hippocampal activity. Systematic exploration of the diencephalon and mid-brain of the cat (Green and Arduini, 1954; Green and Adey, 1955) has shown that the slow-wave trains in the hippocampus can be evoked from many regions of the brain-stem including those "reticular" areas known to be concerned in sleep and wakefulness (Bremer, 1937; Moruzzi and Magoun, 1949). The afferent pathways from these regions to the hippocampus run at least in part through the fornix bundles (Green and Shimamoto, 1953; Green and Arduini, 1954; Green and Adey, 1955).

In view of the evidence for afferent pathways to the hippocampus through the fornix, contrary to the accepted anatomical concepts of impulse flow in the fornix, it is interesting to consider the possibility that the hippocampus may discharge posteriorly into the entorhinal area. While both normal and experimental anatomical material has indicated pathways from the entorhinal area to the hippocampus (Cajal, 1911; Lorente de Nó, 1933; Adey and Meyer, 1952), there is evidence that at least some hippocampal neurons run in the opposite direction to enter the subiculum (Cajal, 1911). The spread of hippocampal seizures to cortical areas also persists after fornix section, suggesting a posteriorly directed efferent hippocampal pathway (Green and Shimamoto, 1953).

Direct stimulation of the entorhinal area produces a prolonged inhibition of upward conduction in certain central tegmental brain-stem pathways which traverse the mesencephalon to the region of the centrum medianum (Adey, Segundo and Livingston, 1955). Moreover the entorhinal area exerts a more powerful influence in this respect than any other cortical area examined in the monkey.

In the present study, behaviour changes have been noted after bilateral resection of the entorhinal area with minimal involvement of the hippocampus and amygdala. Evoked auditory cortical potentials have been studied in response to click and clickless tone stimulation and the trains of late evoked waves compared in intact and operated animals. Auditory cortical responses have been compared with those from the hippocampus in normal and operated animals. Histological examination of the brain-stem after entorhinal ablation has revealed extensive degeneration in mid-brain tegmental areas.

Material and Methods

Twenty-nine specimens of the marsupial phalanger (*Trichosurus vulpecula*) were used in this study. This animal, about the size of a domestic cat, is nocturnal and arboreal. It possesses a prehensile clawed hand and powerful jaws. It is resentful of any handling and, when cornered, attacks vigorously with a concerted clawing and biting movement, standing erect on its hind-limbs.

All cortical ablations were performed with aseptic ritual under nembutal

anæsthesia. The posterior pole of the hemisphere was exposed by removal of a small area of bone adjoining the mid-line. The pia was incised near the posterior pole and the cortex carefully removed with a fine glass-tipped sucker. In this way the cortex medial to the rhinal fissure was revealed and could be removed by progressively deeper suction. The ablations were extended anteriorly to expose the hippocampus, but as far as possible damage to it was avoided. Penicillin was administered for three days after operation.

At the end of the survival period the animals were perfused with formol saline and the brains removed. The extent of the lesions was assessed subsequently by horizontal serial sections stained by the Weigert-Pal method.

Evoked potential studies were performed in animals immobilized with d-tubocurarine administered by the intraperitoneal route. Records were also obtained from two chronic animals with implanted electrodes in the hippocampus following removal of the entorhinal area. In acute experiments head fixation was secured in a Labtronics stereotaxic instrument, and the scalp and adjacent soft tissues infiltrated with procaine. Bipolar silver electrodes with adjustable tip separation of 1–2 mm. were used in cortical recording. Concentric needle electrodes, insulated except adjacent to the tip, were inserted stereotaxically into the dorsal hippocampus. In this way evoked hippocampal and cortical activity could be recorded simultaneously on a double beam oscilloscope. Tektronix type 122 preamplifiers were used as part of a recording system with uniform frequency response from 1 cycle/sec. to 10 kcs/sec.

Auditory stimuli used in the evoked potential studies consisted of clicks and clickless tones delivered from a loudspeaker nine inches from the ear on the same side as the exposed cortex. Clicks were derived from a 1·0 msec. square wave and were delivered with a peak power of 1 watt measured at the voice coil of the speaker. Examination of the reproduced click indicated considerable low amplitude transients for about 10 msec. after the initial deflection. Bursts of tone at frequencies of 500, 1,000 and 2,000 cycles/sec. were also used. The duration of the burst could be varied from 25 to 500 msec. and the rising and falling phases of the burst sloped sufficiently to eliminate any click effect to the human ear. The peak power of the burst as measured above was set at 1 watt. In the systematic cortical explorations only the 25 msec. bursts were used. These carried a distinct tonal quality even at the lowest frequency tested (viz., 500 cycles/sec.).

Degenerative fibres and terminals were sought in the brain-stem following entorhinal ablations in three brains. These animals were killed between the sixth and ninth days after operation. The entorhinal area was removed unilaterally in two animals and in the third the ablation was bilateral. After perfusion in situ, the brains were fixed in 10 per cent

formol saline for one week before frozen sections were cut at a thickness of 15-20μ. At each level sections were stained by the Nauta and Romanes techniques and also by a modified Glees method (Adey and Meyer, 1952b) for purposes of comparison. To assist in identification of major structures at each level, thicker sections cut at 30–40μ were stained by the Weil and Nissl methods. The findings in the operated brains were compared with normal brains stained by the various silver methods.

Results

(1) *Behaviour Studies Following Entorhinal Ablation*

Since facilities for formal psychological testing of such aspects of behaviour as learning capacity were not available, observations have been limited to certain restricted situations, principally those involving reactions to human handling and involving elements of physical insult and provocation. As has been mentioned above, these animals normally resist handling by biting and clawing fiercely.

In the first two or three days following bilateral entorhinal ablation, all animals showed modification of feeding habits. Normally nocturnal, they ate ravenously at any time. At this stage visual defects were present to simple confrontation tests, possibly associated with damage to portion of the occipital cortex during removal of the entorhinal area. Food was located mainly by olfactory cues. Within a week of operation visual acuity had largely returned. The animal's head would follow the observer as he moved about the room and food was once again initially grasped in the forepaws and lifted to the mouth. At this stage the animals sought food only at night, but food offered against the mouth was still occasionally accepted. Two to three weeks after operation food offered in this way was usually refused.

Responses were tested to petting and stroking. The bilaterally operated animals submitted to this freely right from the time of operation and seemed to derive particular pleasure from stroking of the face, making no attempt to bite or claw (fig. 11). Each survival experiment will be described individually, with comparison of the behaviour changes with reconstructions of the cerebral lesions.

Phalanger S1: Survival period twenty-six days following bilateral entorhinal ablation. In the first four days after operation feeding habits were changed as outlined above, but within a week had reverted to nocturnal feeding only. The animal remained docile throughout, showing no aggressive reactions to handling or to provocation with a stick.

Examination of the brain (fig. 1) indicates that on the right side the resection in the upper part of the hemisphere involves the whole of the entorhinal area and extends anteriorly as far as the subiculum. On the left side the dorsal part of the lesion invades the hippocampal pyramidal cell zone slightly. Inferiorly a portion of the entorhinal cortex adjoining

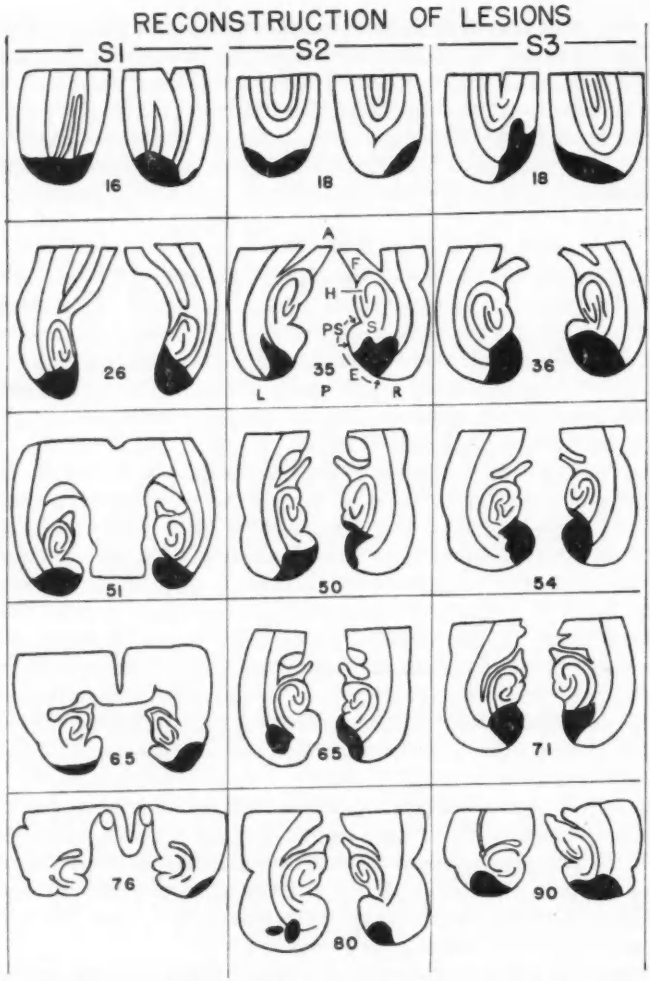

FIG. 1.—Phalangers S1, S2 and S3. Extent of lesions as determined from serial horizontal sections. Representative sections are reproduced in each column and the numbers beneath each section indicate its disposition in the series. The convention adopted for orientation of sections is indicated in section 35 of brain S2 and the major temporo-ammonic structures are shown. Abbreviations: E, entorhinal area; F, fornix; H, hippocampal formation; PS, presubiculum; S, subiculum.

the subiculum is still present, but, as on the right side, this cortex appears to have been virtually isolated from the subjacent white matter. There is no involvement of the amygdala of either hemisphere.

Phalanger S2: Survival period nine days following bilateral entorhinal ablation. This animal could be handled without showing any aggressive tendencies. However, it reacted quite definitely to noxious stimuli, such as prodding with a stick, by rearing on its hind-limbs with fore-limbs raised in an endeavour to bite the stick.

The extent of the ablation was significantly smaller than in the previous experiment. On the right side, much of the inferomedial portion of the entorhinal area adjoining the subiculum remains intact (fig. 1). On the left side almost the whole of the inferior half of the entorhinal area is undamaged. The amygdala is intact in both hemispheres.

It is of interest that this animal showed a smaller but quite definite reduction in aggressive behaviour as compared with S1. This may be correlated with the smaller extent of the lesion in S2.

Phalanger S3: Survival period fifteen days following bilateral removal of the entorhinal area. This animal was extremely tame throughout the survival period. It could be handled freely without provoking any aggressive behaviour. Even when prodded with a stick, or by painful stimulation of the tail or paw, the animal's only reaction was to retreat into the corner of the cage, burying its head between the forepaws. At all times it displayed an intense curiosity about objects such as the examiner's hand which moved in its field of vision. It would stand upon its hind-limbs and lick incessantly at the hand. This curiosity was an obvious trait in other operated animals and is not seen in the intact animal.

Serial sections of the brain (fig. 1) disclosed a virtually complete removal of the entorhinal area on both sides. On the right side a small portion of the subiculum remains inferiorly. Here too, the lesion encroaches slightly into the junctional region between the amygdaloid complex and the entorhinal area, damaging the cortical surface. On the left side a portion of the subiculum, smaller than on right, remains inferiorly. There is no involvement of the amygdala.

Phalanger S4: Survival period six days after unilateral entorhinal ablation. There was no reduction in aggressive behaviour during the short survival period in comparison with pre-operative behaviour.

The extent of the lesion as revealed by the Weigert-Pal method is indicated in fig. 2 and the brain was also examined for degenerating fibres with a variety of silver staining techniques (*vide infra*).

Phalanger S5: Survival period 144 days after bilateral entorhinal ablation. During the first three days after operation this animal had frequent generalized convulsions, often precipitated by external stimuli, such as a flash of light, or a loud click, or by attempts at handling. Between the seizures the animal was irritable, and made clawing and biting movements when approached.

During the next two weeks, it became much tamer and permitted handling. It was, however, very alert to visual stimuli, advancing to

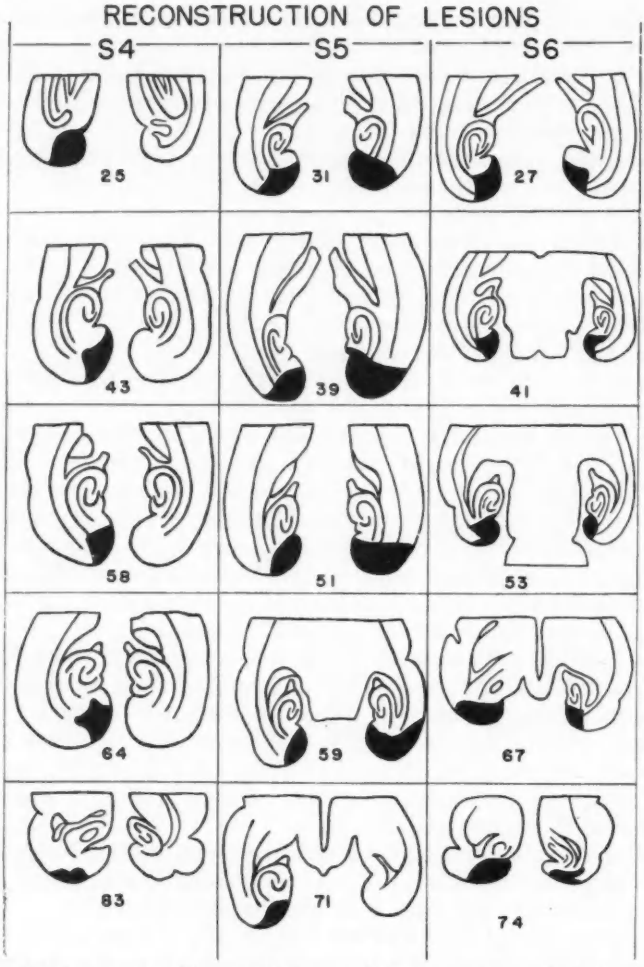

FIG. 2.—Phalangers S4, S5 and S6. Extent of lesions as determined from serial horizontal sections. Arrangement as in fig. 1.

the front of the cage and standing erect to follow movements of the hand. When examined in darkness two weeks after operation, in conditions simulating its normal nocturnal environment, it retreated to the corner of the cage when roughly assaulted with a large cloth bundle and stood with the paws raised above the head. It made no attempt to claw or bite at the bundle.

Six weeks after operation it remained alert and inquisitive, but submitted

freely to all normal handling. It retreated from noxious stimuli without any evidence of aggressive behaviour. Its behaviour pattern remained unchanged during the remainder of the survival period.

Examination of the brain (fig. 2) showed an apparently complete removal of the entorhinal area bilaterally. On the right side a small portion of the presubiculum remains inferiorly. In the left hemisphere the lesion extends inferiorly into the subiculum and also involves slightly the amygdaloid cortex.

Phalanger S6: Survival period 174 days following bilateral entorhinal ablation. This animal was extremely tame right from the time of operation, even under severe provocation. Its only reaction to behavioural insults was to retreat into a corner of the cage and bury the head between the forepaws.

Its behaviour in other respects was interesting. It was markedly inquisitive and enjoyed petting. It showed great pertinacity in enlarging small gaps in the wire cage to effect escape. When these holes were covered with weighted objects of considerable size (up to 3 kgm.) these were gradually displaced to permit egress once more. This retention of important aspects of behavioural drive seemed a clearly separate phenomenon from the reduced aggressiveness following the operation.

In serial section the brain showed an essentially complete removal of the entorhinal area on the left side. On the right side, the lesion spared part of the presubiculum dorsally, but inferiorly the whole of the entorhinal area appears to have been removed and the lesion extends into the subiculum (fig. 2).

Phalanger S7: Survival period seven days following unilateral entorhinal ablation. Throughout the short survival period this animal was at least as vicious as the unoperated animals, fiercely resisting attempts at handling by clawing and biting.

On the ablated side, the resection extended anteriorly as far as the subiculum but the main mass of the hippocampal convolution is intact at all levels. There is a small lesion in the outer cortical layers of the amygdaloid complex in the region adjoining the entorhinal area (fig. 3).

Phalanger S8: Survival period 118 days following a bilateral temporal lesion. This animal's behaviour differed dramatically from the others in the series.

Immediately after recovery from the anæsthetic (about three hours after operation) it attacked viciously with claws and teeth anything placed in contact with its mouth. It systematically bit an apple into small pieces with great vigour, scattering the pieces about the cage and making no attempt to eat them. Provocation with a stick elicited loud and prolonged vocalization and violent biting at the stick.

For several days the animal did not respond to visual stimuli, but with the return of visual acuity the approach of the observer was always

heralded by harsh vocalization and attempts to bite or claw at the hand or any other moving object presented to it. This pattern of behaviour was unvarying throughout the survival period. The animal showed considerable persistence in escaping from small apertures in its cage. After the first few days it no longer attacked food presented to it, but ate normally with a good appetite.

Particular attention was naturally directed to the histological findings in the brain (fig. 8). On the right side the lesion has virtually divided the hippocampus in a coronal plane in its dorsal half. The entorhinal area lying posterior to the division is intact except at its medial end. Inferiorly on the right side the lesion is restricted to the deeper parts of the hippocampus and involves slightly the presubiculum. There is a small lesion in the amygdaloid cortex. On the left side a small amount of the medial end of the entorhinal area has been removed throughout the whole vertical extent of the area which is otherwise intact. There is a small amygdaloid cortical lesion inferiorly.

Phalanger S9: Survival period thirty-three days after bilateral entorhinal ablation. This animal submitted to handling throughout the post-operative period without any aggressiveness. However, in the face of behavioural insults it showed some resentment, although at a higher threshold than in unoperated animals.

Examination of the brain (fig. 3) showed that the entire entorhinal cortex had been removed bilaterally, and that inferiorly the lesion extended into the hippocampal formation, particularly on the left side. Inferiorly the lesion involves the amygdaloid cortex on both sides, to a greater degree on the right side than the left.

Phalanger S10: Survival period seven days following bilateral entorhinal ablation. This animal responded pleasurably to petting twenty-four hours after operation and remained tame throughout the survival period. When provoked with a stick, it retreated to the corner of the cage and buried its head between the forepaws.

Histological examination of its brain (fig. 3) indicated an apparently complete resection of the entorhinal area, not significantly involving the hippocampus, although removing the subiculum on the right side. On the left side there is a small cortical lesion in the amygdala adjoining the entorhinal area.

Thus bilateral removal of the entorhinal area appears to be followed by a significant reduction in the aggressive responses to noxious and insulting stimuli normally seen in the phalanger. In addition, the operated animals display a deep curiosity towards moving objects, at which they sniff persistently. This curiosity is not seen in the unoperated animals. Despite the tameness, they are capable of sustained and purposeful attention to such activities as engineering escape from their cages. The reduction in aggressive behaviour was less obvious where the lower

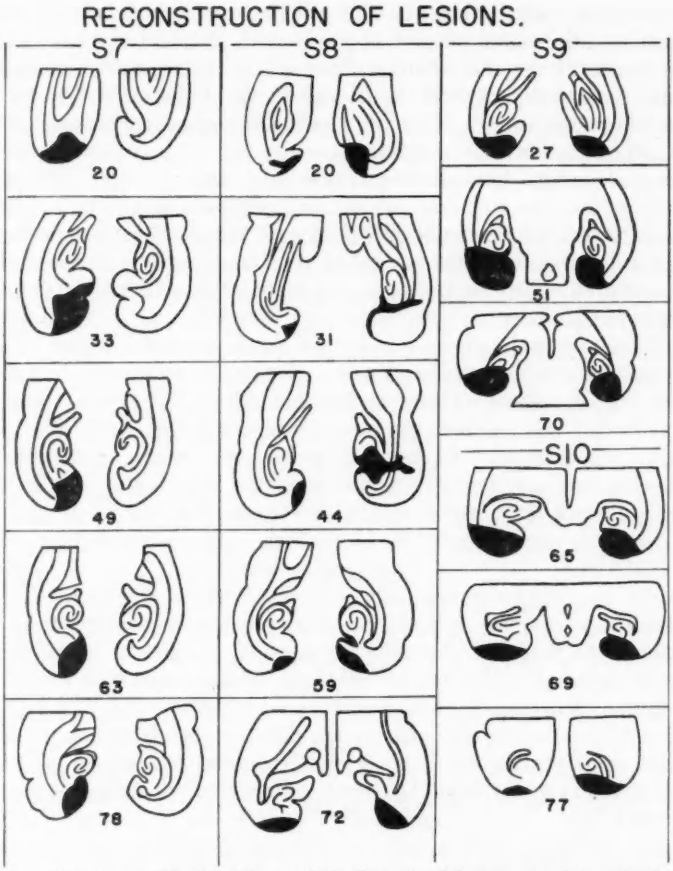

FIG. 3.—Phalangers S7, S8, S9 and S10. Extent of lesions as determined from serial horizontal sections. Arrangement as in fig. 1.

part of the entorhinal cortex remained intact (S2), and in the one animal where slight damage to the entorhinal area was accompanied by significant damage to the hippocampus and some involvement of the amygdala (S8), the animal became extremely ferocious until sacrificed four months after operation, its aggressiveness far exceeding that of the unoperated animals.

(2) *Electrophysiological Studies*

In view of the considerable changes in emotional responses following bilateral removal of the entorhinal area in the phalanger, it was decided to test the effects of an auditory stimulus on the evoked auditory cortical potentials in ablated animals. It has been observed in normal animals that

there are significant differences in the form of both the primary evoked response and the ensuing trains of slow waves, depending on the state of sleep or wakefulness of the animal (Bremer, 1954). Moreover, an auditory stimulus is normally capable of "blocking" the alpha rhythm in the conscious but resting animal, replacing it with the rapid asynchronous activity described as an "arousal" response.

Our explorations have all been made in conscious curarized animals. Since most previous explorations of the auditory cortex have been made under barbiturate anæsthesia (Woolsey and Walzl, 1942; Tunturi, 1944; 1950 *a* and *b*) or with the *encéphale isolé* preparation (Bremer, 1943) a series of preliminary explorations was made of the extent of the auditory cortex in the phalanger.

(*a*) *Extent of the auditory cortex and the form of the responses in the intact animal.*—Within the responsive zone the spontaneous and evoked activity varied widely. Using click stimulation, the evoked potentials were recorded with bipolar electrodes oriented in the horizontal plane. The zone was essentially the same in peripheral extent in seven mappings. The cortex was continuously responsive from the vicinity of the rhinal fissure anteriorly in a region which overlapped the second somatic area (*vide infra*) to the posterior border of the hemisphere behind (fig. 4, Plate XXXV).

The primary response was usually largest in the cortex near the centre of the responsive area. It was here, too, that the slower wave-like components of the response showed their greatest complexity. The primary response appeared with a latency of 10 to 15 msec. and its duration with the bipolar recording method was about 25 msec. Attention has been directed particularly to the later responses occurring up to several seconds after the primary deflection, since these later modifications in the pattern of background activity might be correlated with the physiological processes of alerting.

In this connexion there are some interesting differences in the character of the spontaneous activity in different parts of the auditory cortex in the curarized animal. Antero-inferiorly, in a region which largely overlapped somatic area II, the bipolar record was characterized by very rapid spontaneous activity. Here the primary evoked auditory response was not followed by significant modification of this rapid cortical discharge, and no slow waves followed the primary response. In the central and posterior parts of the responsive zone spontaneous activity was usually slower and, following the primary response, showed one or two fairly constant slow deflections in the ensuing 100 to 200 msec. The presence of these slow waves in this region seemed related to the general state of arousal of the animal, since when first placed in the stereotaxic instrument or if subjected to noxious stimuli, these slower components tended to disappear in spontaneous rapid activity of low amplitude, and the primary response was likewise smaller, as noted by Bremer (1953).

Using bursts of clickless tone at 500, 1,000 and 2,000 cycles/sec. and lasting 25, 50 and 100 msec. at each frequency, no evidence of a tonotopic organization of the auditory cortex could be found.

(*b*) *Effects of entorhinal ablation on the evoked auditory responses.*—The most striking changes were seen in the nature of the late evoked potentials in the central and more dorsal parts of the responsive area. It is stressed that these changes were sought only in chronic animals 7 to 174 days after the cortical resection.

In all these animals bursts of "spindles" with a period of about 100 msec. followed the primary response. The initial spindle occurred with a latency of about 30 msec. following the primary response. Five to ten spindles occurred in each burst (fig. 5). These spindle bursts could be elicited in most operated animals within a few minutes of being placed in the stereotaxic instrument, whereas in the unoperated animals they were usually not observed at all, or, as in 2 cases, were seen only after the animal had been in the stereotaxic instrument for many hours.

(*c*) *Effects of combined auditory and somatic stimulation on evoked responses in somatic area II.*—It has already been noted that primary evoked auditory responses recorded in somatic area II in normal animals were not followed by the trains of slow-waves seen more posteriorly in the responsive area. It was therefore decided to test the extent of possible interaction between auditory and somatic responses in this area.

Compared with the responses to somatic stimulation in this area evoked in the phalanger under nembutal anæsthesia (Adey and Kerr, 1954), the responses in the curarized animal showed much greater variability in form, occurring against a background of rapid spontaneous activity. Fig. 6 shows the effects of varying spacing betweeen the auditory and ensuing somatic stimulus to the ipsilateral forepaw. It will be seen that, with bipolar cortical electrodes spaced 2 mm. horizontally, the auditory and somatic responses are in opposite phase. There is no evidence of occlusion of the somatic by the auditory response over the range of shock spacings 20 to 150 msec. At a shock spacing of 20 msec. the somatic response appears on the falling phase of the auditory response and is not appreciably reduced in size over the control response.

(*d*) *Responses to auditory stimulation recorded in the hippocampus following entorhinal ablation.*—Concentric electrodes were inserted stereotaxically into the dorsal hippocampus on one or both sides of the brain immediately prior to sacrificing animals used in behaviour studies after entorhinal ablation. In two of these animals records were also taken with chronically implanted hippocampal electrodes. Typically the unstimulated hippocampal record in these animals showed irregular slow activity. Auditory stimulation evoked a large primary response followed by one or more slow-waves (figs. 7 and 8, *see* Plates).

These evoked slow-waves are well illustrated in fig. 5, in response to a

series of click (A and B) and hand-clapping stimuli (C and D) spaced approximately thirty seconds apart. In this case it is apparent that the slow-wave train rapidly adapts, although the primary hippocampal response persists throughout. Here, too, the trains of cortical spindles following the primary evoked response are particularly obvious.

By contrast with the hippocampal record in the unstimulated tame animal, an animal showing unremitting savage behaviour for a period of four months after operation (S8), exhibited almost unceasing trains of slow-waves in its hippocampus (fig. 8). These trains were enhanced by any minor stimulus such as passive manipulation of the limbs while immobilized in the stereotaxic instrument.

The findings thus suggest that both the hippocampal primary and slow-wave responses persist after removal of the entorhinal area, and thus provide confirmatory evidence that this form of hippocampal excitation occurs through some route other than from the entorhinal area.

(3) *Experimental Histological Studies of Efferent Pathways from the Entorhinal Area*

It is felt that particular care must be exercised in the assessment of degeneration detected by any of the various silver techniques currently used. The pitfalls of both false positives and negatives may be difficult to avoid. The results presented here have been carefully assessed by comparison of results from Nauta, Glees and Romanes techniques and also by the staining of normal material.

It would appear that scattered fibres can be detected in normal material which show the discontinuity and argentophilia considered characteristic of degenerating material. In our experience these fibres are very sparsely distributed in normal material and do not form part of a consecutive neural pathway. It appears, however, that their members can be exaggerated by the use of any lipoid anæsthetic agent in sacrificing the animal. All our animals have therefore been killed by perfusion under barbiturate anæsthesia.

Since an appearance of degeneration in normal material seems more common in fine fibres adjoining the free surface of the brain, there is a particular problem in the assessment of degeneration in such bundles as the stria medullaris. In this instance, however, we consider that the very scattered beading noted in our normal preparations presents a basically different picture from the massive degeneration of the stria seen following entorhinal ablation. In our hands the Nauta method gives more consistent results with greater ease of interpretation than either Glees or Romanes techniques.

(*a*) *Section at the level of the anterior commissure.*—Transverse sections at this level nine days after bilateral removal of the dorsal half of the entorhinal area (S2) show clearly numerous degenerating fibres sweeping

ventrally into the posterior part of the anterior commissure from the lower half of the external capsule on the lateral side of the lentiform nucleus. At this level the anterior commissure is divisible into dorsal and ventral portions, the dorsal portion passing at its lateral extremities into the region of the internal capsule between lentiform and caudate nuclei, while the ventral portion skirts below the lentiform nucleus to become continuous with the external capsule.

Degenerating fibres were almost solely confined to the ventral part of the anterior commissure. In this case, the lesion was much more extensive on the right than the left side and there is a correspondingly larger amount of degeneration in the right external capsule and the right side of the anterior commissure. The degeneration decreases sharply on the left side of the mid-line, suggesting that a considerable portion of the degenerating fibres leave the commissure in the vicinity of the mid-line (fig. 9).

In the dorsal part of the anterior commissure occasional isolated fibres situated in the lateral part of the commissure show degeneration. The hippocampal commissure at this level is free of degeneration.

In view of these findings longitudinal sections were cut adjoining the mid-line.

(*b*) *Paramedian sections through the diencephalon and mid-brain.*— In two brains with unilateral entorhinal ablations (S4 and S7, survival period six and seven days respectively) longitudinal sections were cut from both sides of the brain adjacent to the mid-line to include all structures lying rostral to the superior collicular level. In this way the stria medullaris system was fully displayed.

The stria medullaris bundles of both hemispheres were extensively disrupted following a unilateral entorhinal lesion. The disrupted bundles could be traced from the vicinity of the anterior commissure over the dorsal surface of the thalamus to the pretectal region. Here they dipped sharply into the deeper layers of the tectum, passing ventrally as well as caudally in the mid-brain. The disruption of fibres involves those quite deeply situated as well as those running adjacent to the surface of the stria. It appears that the degeneration is more extensive in the ipsilateral stria (fig. 9).

To exclude as far as possible the incidence of artefacts in assessing the degeneration, the results have been compared with similarly stained material from unoperated perfused brains (fig. 10). In the unoperated brains there were occasional scattered disrupted fibres resembling those in the operated brains. However, they were widely dispersed and did not exhibit the intense argentophilia of the numerous disrupted fibres in the operated brains. The majority of the fibres of the stria medullaris in the unoperated brains show no abnormality.

These longitudinal sections also show clearly a considerable number of heavily degenerating fibres entering the septal area from the vicinity

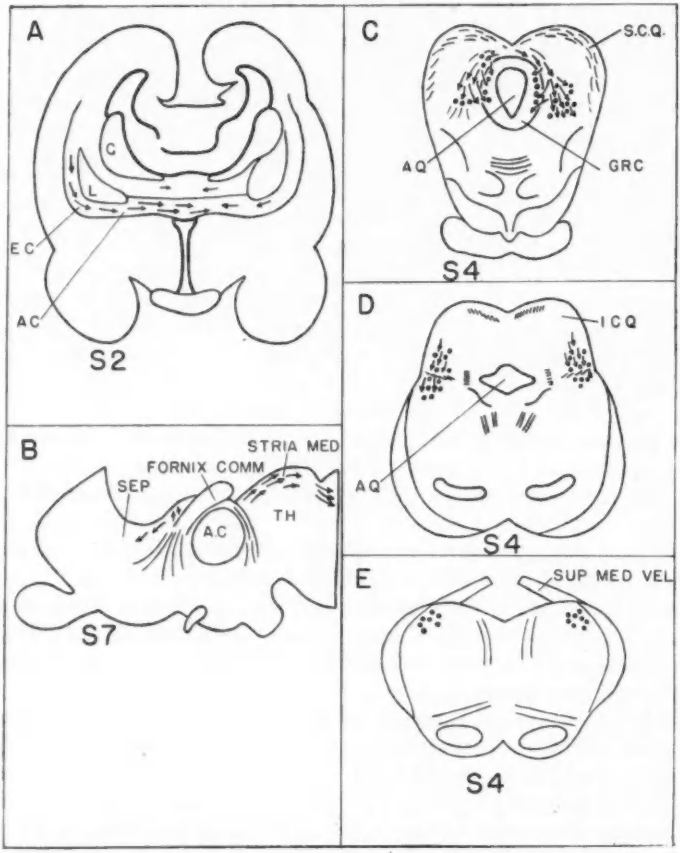

FIG. 9.—Diagrammatic arrangement of the course taken by degenerating fibres from the entorhinal area in specimens S2, S4 and S7; fibres indicated by arrows and degenerating terminals by dots. A, C, D and E: transverse sections at the level of the anterior commissure (A), superior colliculi (C), inferior colliculi (D) and superior medullary velum (E). B: longitudinal paramedian section through the diencephalon. Abbreviations used: AC, anterior commissure; AQ, cerebral aqueduct; C, caudate nucleus; EC, external capsule; FORNIX COMM, fornix commissure; GRC, central grey matter; ICQ, tectum of inferior colliculus; L, lentiform nucleus; SEP, septal area; SUP MED VEL, superior medullary velum; TH, thalamus.

of the precommissural fornix. Degenerating terminals are present amongst the cells of the dorsal and posterior parts of the septum.

(*c*) *Transverse sections through the mid-brain.*—In three brains, two with unilateral and one with bilateral entorhinal ablations (S4, S7 and

S2, survival period six, seven and nine days respectively) transverse sections have been examined from the upper levels of the mid-brain to the pons inferiorly.

Sections through the superior colliculus show degenerating fibres fanning out as an arch on both sides of the brain from the vicinity of the mid-line dorsally. These fibres can be traced ventrally on each side of the tube of central grey matter, and send a number of fine degenerating terminal filaments amongst the more laterally placed cells of the central grey matter. This arcade of degenerating fibres is sharply marked off laterally from the more superficial regions of the tectum and dorsal tegmentum, which show no degeneration. The degeneration can be traced ventrally to a level approximating the ventral border of the cerebral aqueduct, but more ventral regions of the tegmentum show no degeneration. The degeneration is almost symmetrical on the two sides in brains with unilateral lesions (fig. 9). No similar disruption of fibres could be found in normal material.

More caudal sections at the level of the inferior colliculus show a similar distribution of bilateral degeneration in the lateral parts of the dorsal tegmentum following a unilateral resection of the entorhinal area. Here there are degenerating fine fibres with numerous swollen terminals surrounding the nerve cells. Sections further caudally at the level of the superior medullary velum show only scattered swollen terminals in this region, and although these cannot be regarded as unequivocal evidence of degeneration in view of their close resemblance to the discrete spheroidal bodies seen in normal tissues stained by the Nauta and Glees techniques, they were not present in other parts of the section.

Thus in summary it appears that there is histological evidence of a major pathway running from the entorhinal area through the external capsule to the anterior commissure, thence distributed bilaterally through the stria medullaris to the dorsal tegmental regions of the mid-brain.

Discussion

(*a*) *Behaviour studies.*—Complete bilateral temporal lobectomy in the monkey leads to the profound changes in behaviour described by Klüver and Bucy (1939). The animals show great tameness, an intense curiosity with oral tendencies, a lack of appreciation of the significance of objects examined and particularly of their potentially dangerous character. They also exhibit a loss of social behaviour and are hypersexual. Klüver has coined the term "psychic blindness" to cover the major aspects of the behaviour defects.

Attempts have been made to differentiate the various aspects of this disordered behaviour pattern by resection of limited portions of the temporal lobe. There are certain inconsistencies in the reports of behaviour changes following these restricted ablations, probably due in part to the

technical difficulties involved in localized resection without significant damage to adjoining structures.

Resection of the amygdaloid complex (Bard and Mountcastle, 1948; Anand and Brobeck, 1952; Gastaut, 1952; Schreiner and Kling, 1953) was reported by Bard and Mountcastle to be followed in the cat by relatively permanent rage and savageness which developed gradually several weeks after placement of the lesions in a limited series of experiments. More recently Schreiner and Kling noted that amygdaloid ablation in a larger series of cats was followed by irritability in only two out of twenty animals, the remainder showing increased motor activity in response to visual stimuli, exaggerated oral and vocal behaviour, relative docility and a state of hypersexuality. The most obvious changes were in the fields of affective behaviour and sexuality. Here again the picture is complicated by the observation of Schreiner and Kling that an enraged state followed administration of stilbœstrol to amygdalectomized animals, suggesting that the amygdala is involved in endocrinological phenomena and that the phases of the sex cycle may play a part. Stimulation of the amygdala in the conscious human is followed by profound alterations in consciousness (Penfield, 1954), and if carried to the point of an amygdaloid seizure with after-discharge, is accompanied by automatic behaviour as seen in psychomotor epilepsy.

Removal of the hippocampus alone is a technically difficult procedure without incurring considerable damage to temporal cortex, but is said to lead to increased pleasure reactions in the cat (Bard and Mountcastle, 1948) and to be followed in the monkey by less impairment of visual discrimination performance than is seen after removal of parts of the entorhinal area and adjacent inferior temporal lobe cortex (Mishkin, 1954). Stimulation of the hippocampus indicates a very low seizure threshold (Gibbs and Gibbs, 1936; Renshaw, Forbes and Morison, 1940; Jung, 1949; Kaada, 1951; Green and Shimamoto, 1953), and in the conscious animal is accompanied by an "arrest reaction" resembling *petit mal*, with abrupt cessation of activity and vacant staring (Andy and Akert, 1955). A similar arrest reaction follows stimulation of the fornix (Hunter, 1950; Kaada and Jasper, 1952). Its very low seizure threshold suggests that it may participate in the mechanism of epileptic seizures (Jasper and Kershman, 1941; Liberson *et al.*, 1950, 1951, 1952, 1955; Scoville *et al.*, 1953).

The profound tractability which we have noted in the phalanger after removal of the entorhinal area and the curiosity which these operated animals display resemble in many respects the elements of behaviour change seen after more extensive temporal lobectomies. Despite their tameness, these animals retain a considerable capacity for sustained and directed behaviour, as in escaping from their cages. In this respect their behaviour may differ from that following extensive bilateral temporal

lobectomy, where much time may be spent in aimless re-examination of objects already examined a short time previously.

Recent careful studies of the effects of removal of the ventral areas of the temporal lobe, including the inferior temporal gyrus, the entorhinal area and the hippocampal formation (Mishkin, 1954; Mishkin and Pribram, 1954; Mishkin and Hall, 1955; Pribram and Mishkin, 1955) have shed much light on the role of these areas in visual discrimination. It was found that resections involving the inferior temporal, fusiform and posterior hippocampal gyri in the macaque produced a markedly greater impairment of visual discrimination than did removal of the hippocampus or control lesions in other parts of the temporal cortex. These workers concluded that the decrement in visual discrimination was a function of the situation determining the differential response, impairment being found in tasks which differed from others previously learnt only in the manner in which the identical discriminanda were presented. They point out that an additional factor may be involved in view of the inability of the operated animals to discriminate fine changes in the physical size of the test objects.

While these results point to the inferior temporal cortex as intimately concerned in the interpretation of highly complex visual afferent data, it is of interest that there were no consistent post-operative effects with other tests, nor were changes in affective behaviour noted. Examination of the reconstructions of the lesions in their experiments suggests that they spared much of the entorhinal area. Our results in the phalanger where much of the entorhinal area remained (S2 and S8) likewise indicated little or no modification of affective responses. In all our animals with an essentially complete removal a marked decrease in affective responses was observed.

(*b*) *Rhinencephalic mechanisms in the "alerting" response.*—The well-known phenomenon of "alpha blocking" associated with the direction of the attention in man and animals can be simulated by electrical stimulation of the central tegmental areas of the mid-brain and certain areas of the thalamus (French, Amerongen and Magoun, 1952). This desynchronization of the alpha rhythm during alerting or arousal is accompanied by a slow synchronous discharge at 2 to 5 waves per second in the hippocampus, resembling in many respects the theta rhythms recorded in the temporal leads of children and emotionally immature adults. Restricted lesions in the central mid-brain tegmentum without involvement of the lemniscal systems lead to a condition resembling profound sleep, with constricted pupils, regular respiration and only momentary arousal to noxious stimuli. The cortical record shows recurrent spindling as in normal sleep (Whitlock, Arduini and Moruzzi, 1953).

Peripheral stimulation of somatic, auditory or visual modalities produces a double response in the hippocampus. There is a sharp primary response, succeeded by one or more slow-waves varying in frequency from 2 to 5

per second (Gerard, Marshall and Saul, 1936; Jung and Kornmüller, 1939; Maclean, Horwitz and Robinson, 1952; Liberson and Cadilhac, 1953; Green and Arduini, 1954; Green and Adey, 1955). Green and Arduini noted that stimulation of the reticular areas of the brain-stem, including various parts of the mid-brain tegmentum, hypothalamus, the intralaminar nuclei of the thalamus, the pre-optic region and septum produced the slow-wave response in the hippocampus. These findings suggested extensive connexions between the hippocampal formation and those subcortical regions which appear concerned in the arousal response, such as the intralaminar thalamic nuclei and the tegmental areas of the mid-brain, and that the fornix might provide a pathway for the entry of these impulses into the hippocampus from the diencephalon. This is supported by the finding that lesions in the septum and fornix blocked the slow-wave response (Green and Arduini, 1954).

Careful assessment of excitability thresholds in the diencephalon has indicated that the fornix has the lowest threshold for the production of the hippocampal slow-waves and that these do not appear to result from antidromic conduction in the fornix (Green and Adey, 1955). This afferent pathway appears to run caudally deeply within the hippocampus, since section of the alveus on the hippocampal surface does not abolish the response elicited by fornix stimulation. Moreover, examination of the responses in the hippocampus to fornix stimulation during progressive penetration of the hippocampus by the recording electrodes has indicated a deeply situated "turnover" point for the short latency response, the evidence also suggesting the dentate fascia as an intermediary relay station on the afferent pathway from the fornix to the hippocampal pyramidal cells (Green and Adey, 1955).

There is thus considerable physiological evidence supporting the concept of a caudally directed inflow to the hippocampus via the fornix bundles, and it is supported by the anatomical studies of Gerebtzoff (1941–42) Sprague and Meyer (1950) and Morin (1950). Such a caudally directed inflow would run in the opposite direction to the classical pathways through the hippocampus described by Cajal (1911), who concluded that afferent fibres enter the hippocampus from the entorhinal area of Brodmann, from the cingulate region via fibres of the cingulum bundle, from the supracallosal striæ and from the contralateral hippocampus. He considered that hippocampal efferent fibres arose from the pyramidal cells, entered the fimbria and then passed either into the opposite hippocampus via the hippocampal commissure or into the fornix system to be conveyed to the septum, hypothalamus, anterior thalamus and more caudal parts of the brain-stem.

This classical concept has gained support from the studies of Lorente de Nó (1934), Adey and Meyer (1952 *a* and *b*), Simpson (1952), Sprague and Meyer (1950), Daitz and Powell (1954) and Powell and Cowan

(1954, 1955) so that it is possible that the hippocampus may be accessible to impulses from both the fornix anteriorly and the entorhinal area posteriorly. The possibility that the entorhinal cortex and temporo-ammonic tracts may modify the general level of excitability within the hippocampus has been discussed elsewhere (Green and Adey, 1955).

Our results, confirmed by histological examination, have indicated that the slow-wave hippocampal response can be recorded in the absence of the entorhinal cortex. These results are in agreement with those of Ricci and Sutin (personal communication) and those of Green and Arduini (1954) that substantial or complete removal of the entorhinal cortex is not followed by loss of the slow-wave response in the hippocampus. Recently Carreras *et al.* (1955 *a* and *b*) have suggested that the entorhinal cortex and temporo-ammonic tracts may be directly concerned in hippocampal "arousal," but our results in chronic animals have indicated that the hippocampal responses to peripheral stimulation are still present after entorhinal ablation, provided ample time has been allowed for recovery from cerebral shock.

In a survey of corticifugal influences on upward conduction in certain pathways of the central tegmental areas of the brain-stem in the cat and monkey, it was found that the basal occipitotemporal cortex, and particularly the entorhinal area, was capable of exercising a more profound influence on upward conduction in the tegmentum than any other cortical area (Adey, Segundo and Livingston, 1955). A single cortical shock lasting one-tenth millisecond was capable of modifying reticular conduction for as long as two seconds.

Since the hippocampus can be activated via the fornix from stimulation of the thalamus and septum, and since the entorhinal area can greatly modify central tegmental conduction at the mid-brain level through seemingly defined anatomical paths (*vide infra*), it may be suggested that the hippocampus plays a part in a caudally directed circuit running from the septum and intralaminar nuclei of the thalamus through the fornix to the hippocampus, thence to the entorhinal area and so to the mid-brain tegmentum via the stria medullaris bundles.

Such a pathway might well be of a re-entrant type. The reticular thalamic, hypothalamic and septal areas of the diencephalon are themselves activated by a wide variety of sensory stimuli and form part of a "non-specific" cortical activating system. The hippocampus may in turn send impulses through the entorhinal area to the mid-brain tegmentum, where they may initiate further modification in the upward stream of neural activity in the reticular formation (Adey, 1955 *a* and *b*).

The least known link in such a chain of connexions is from the hippocampus to the entorhinal area. Cajal (1911) observed fibres entering the subiculum from the hippocampus in addition to those running the accepted course of the temporo-ammonic tracts. He suggested that the fibres

might be responsible for a reciprocal innervation between the two structures, but regarded this as unlikely. He believed that the subiculum might give rise to a projection tract with a destination as yet undetermined, but which might run the initial part of its course in the fimbria.

The spindle trains which we have consistently observed following the primary response in the auditory cortex after entorhinal ablation appear to indicate a subtle change in the normal cortico-diencephalic relationships. Bremer (1945) has noted similar trains of slow-waves following the primary auditory cortical response in *encéphale isolé* preparations and has correlated the phenomenon with the onset of sleep in these animals. The appearance of these evoked spindle trains may well indicate a waning consciousness or perhaps more precisely a diminution of alerted or directed attention, for we have noted them in normal animals after many hours of intermittent auditory stimulation in the stereotaxic instrument. Gerebtzoff (1941) noted spontaneous spindling at 6 to 9 per second in cats and rabbits under hypnosis induced by exposure to bright lights or by various postural manœuvres. He also noted spindle trains in these animals in the auditory cortex following the primary response to click stimulation.

Generalized cortical spindling is seen in normal sleep and follows lesions in the mid-brain tegmentum (Bremer, 1935; Whitlock, Arduini and Moruzzi, 1953). Profound changes in consciousness follow lesions in this region in man (Cairns, 1952), suggesting that these tegmental areas ("reticular formation") are intimately concerned in mechanisms of sleep and wakefulness. Our histological evidence indicates that considerable numbers of fibres from the entorhinal area terminate in the lateral parts of the mid-brain tegmentum. The removal of a tonic influence in this region may account for the cortical spindling seen in our experiments.

It is of particular interest that Gloor (1955 *a* and *b*) has observed short latency responses from amygdaloid stimulation in the same regions of the lateral mid-brain tegmentum as those in which fibres from the entorhinal area appear to terminate in our experiments. Gloor points out that these responses appear with a much shorter latency than those recorded in the immediately rostal regions of the posterior hypothalamus. In the light of our histological findings these short-latency responses from the amygdala may also pass caudally in the stria medullaris, since the stria medullaris receives some fibres from the stria terminalis bundles which arise in the amygdala (Johnston, 1923).

(*c*) *Histological findings after entorhinal ablation.*—It has been stressed in the account of the degeneration noted in our experiments that certain difficulties attach to the interpretation of silver-impregnated material, but that these difficulties do not appear to invalidate the methods, provided that certain criteria and controls are imposed. In our experience these

methods may show in normal material scattered fibres closely resembling fine degenerating fibres, but this scattered type of "degeneration" does not usually lead to confusion. It does, however, point to the need for care in assessing scattered fibre and terminal degeneration occurring as an isolated phenomenon.

The stria medullaris is phylogenetically very old, with all its principal connexions present in the amphibian (Huber and Crosby, 1926), where fibres can be seen passing caudally from the primordial pyriform cortex to enter the stria medullaris, thus constituting the lateral olfactohabenular tract (Herrick, 1927). In reptiles this tract arises from the amygdaloid complex and to a variable extent from the cortex of the pyriform lobe. In both amphibians (van Gehuchten, 1897) and reptiles, this tract appears to send relatively few of its fibres into the habenula, but rather decussates in the habenular commissure and, retracing its course, is distributed to areas homologous with those from which it arose (Ariens Kappers, Huber and Crosby, 1936). Similar pathways from the pyriform cortex of mammals have been described by many early workers (Ganser, 1882; Lotheissen, 1894) although their existence was denied by Cajal (1911).

There is thus substantial agreement concerning the entry of fibres from the pyriform cortex into the stria medullaris bundles in all vertebrates. Yet no evidence appears to have been adduced hitherto suggesting their continued passage caudally beyond the habenular region into the mid-brain tegmentum.

Summary

(1) The entorhinal area has been studied in the marsupial phalanger (*Trichosurus vulpecula*). It has been removed by a procedure causing minimal damage to the hippocampus and amygdaloid complex.

(2) Bilateral resection of the entorhinal area is followed by an immediate and sustained reduction in the phalanger's normally aggressive responses to handling or provocation by noxious stimulation. Unilateral removal of the area does not significantly modify the aggressive behaviour. Animals with a bilateral ablation also exhibit a profound curiosity not seen in the intact animal and are aroused particularly by moving objects. Although displaying considerable tameness after bilateral resection of the entorhinal area, the phalanger still appears capable of sustained and directed attention.

(3) Evoked potential studies have been made in ablated and intact animals of the hippocampal and auditory responses to click and tone stimulation. No evidence of a tonotopic organization of the auditory cortex could be found in curarized animals, nor could occlusion ("blocking interaction") be detected between auditory and somatic responses in somatic area II.

(4) Records from the hippocampus following bilateral removal of the entorhinal area continue to show both primary responses and slow-wave

trains in response to auditory stimulation. Simultaneous records from the auditory cortex usually show trains of spindles at 8 to 10 per second following the primary response in the ablated animals. Such spindle-trains have been sought in unoperated animals but have been seen only rarely, and then only after exposing the animal to continuous stimulation for many hours. The relationship of these spindles to those seen in normal sleep and in mid-brain lesions is discussed.

(5) Experimental histological studies of the efferent pathways from the entorhinal area by silver impregnation methods strongly suggest direct connexions between the entorhinal area and the tegmental regions of the mid-brain. This pathway runs initially via the external capsule into the anterior commissure and is then distributed bilaterally through the stria medullaris, coursing posteriorly on the dorsal surface of the thalamus. The fibres terminate in the dorsal tegmentum of the mid-brain adjoining the periaqueductal grey matter.

(6) The role of the hippocampus in the process of alerting is discussed in the light of these and other studies. It is suggested that the hippocampus may be connected with deep centres in the diencephalon and mid-brain (the so-called "reticular areas" of the brain-stem) by two routes. The hippocampus is activated from the septum and intralaminar nuclei of the thalamus via the fornix bundles. It is suggested that the hippocampus may project via the entorhinal area to the mid-brain tegmentum by way of the stria medullaris, thus forming part of a re-entrant pathway into the reticular formation, which is itself powerfully concerned in sleep and wakefulness.

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REFERENCES

ADEY, W. R. (1955*a*) *J. Anat. Soc. India*, **4**, 27.
—— (1955*b*) *Med. J. Aust.* In press.
——, and KERR, D. I. B. (1954) *J. comp. Neurol.*, **100**, 597.
——, and MEYER, M. (1952*a*) *Brain*, **75**, 358.
——, and MEYER, M. (1952*b*) *J. Anat., Lond.*, **86**, 58.
——, SEGUNDO, J. P., and LIVINGSTON, R. B. (1954) *Amer. J. Physiol.*, **179**, 613 (abstract).
ANAND, B. K., and BROBECK, J. R. (1952) *J. Neurophysiol.*, **15**, 421.
ANDY, O. J., and AKERT, K. (1955) *J. Neuropath.*, **14**, 198.
ARIENS KAPPERS, C. U., HUBER, C. G., and CROSBY, E. C. (1936) "The Comparative Anatomy of the Nervous System of Vertebrates, including Man." New York. Vol. 2.

BARD, P., and MOUNTCASTLE, V. B. (1948) *Res. Publ. Ass. nerv. ment. Dis.*, **27**, 362.
BREMER, F. (1935) *C. R. Soc. Biol.*, Paris, **118**, 1235.
—— (1937) *Bull. Acad. R. Méd. Belg.*, **2**, 68.
—— (1943) *Arch. int. Physiol.*, **53**, 53.
—— (1953) "Some Problems in Neurophysiology." London.
—— (1954) The neurophysiological problem of sleep. *In* "Brain Mechanisms and Consciousness." A symposium organized by The Council for International Organizations of Medical Sciences. Oxford, p. 137.
CAIRNS, H. (1952) *Brain*, **75**, 109.
CARRERAS, M., MACCHI, G., ANGELERI, F., and URBANI, M. (1955*a*) *Boll. Soc. ital. Biol. sper.*, **31**, Sep.
——, MACCHI, G., ANGELERI, F., and URBANI, M. (1955*b*) *Boll. Soc. ital. Biol. sper.*, **31**, Sep.
DAITZ, H. M., and POWELL, T. P. S. (1954) *J. Neurol. Neurosurg. Psychiat.*, **17**, 75.
FRENCH, J. D., VON AMERONGEN, F. K., and MAGOUN, H. W. (1952) *Arch. Neurol. Psychiat., Chicago*, **68**, 577.
GANSER, S. (1882) *Morph. Jb.*, **7**, 591.
GASTAUT, H. (1952) *J. Physiol., Paris*, **44**, 431.
GEHUCHTEN, A. VAN (1897) *Bull. Acad. R. Sci. Belg.*, **34**, 38.
GERARD, R. W., MARSHALL, W. H., and SAUL, L. J. (1936) *Arch. Neurol. Psychiat., Chicago*, **36**, 675.
GEREBTZOFF, M. A. (1941–42) *J. belge. Neurol.*, **41–42**, 199.
—— (1941) *Arch. int. Physiol.*, **51**, 365.
GIBBS, F. A., and GIBBS, E. L. (1936) *Arch. Neurol. Psychiat., Chicago*, **35**, 109.
GLOOR, P. (1955*a*) *Electroenceph. clin. Neurophysiol.*, **7**, 223.
—— (1955*b*) *Electroenceph. clin. Neurophysiol.*, **7**, 243.
GREEN, J. D., and ADEY, W. R. (1955) *Electroenceph. clin. Neurophysiol.* In press.
——, and ARDUINI, A. A. (1954) *J. Neurophysiol.*, **17**, 533.
——, and SHIMAMOTO, T. (1953) *Arch. Neurol. Psychiat., Chicago*, **70**, 687.
HERRICK, C. J. (1927) *J. comp. Neurol.*, **43**, 231.
HUBER, G. C., and CROSBY, E. C. (1926) *J. comp. Neurol.*, **40**, 97.
HUNTER, J. (1950) *Electroenceph. clin. Neurophysiol.*, **2**, 193.
JASPER, H. and KERSHMAN, J. (1941) *Arch. Neurol. Psychiat., Chicago*, **45**, 903.
JOHNSTON, J. B. (1923) *J. comp. Neurol.*, **35**, 337.
JUNG, R. (1949) *Arch. Psychiat. Nervenkr.*, **183**, 206.
——, and KORNMÜLLER, A. E. (1938) *Arch. Psychiat. Nervenkr.*, **109**, 1.
KAADA, B. R. (1951) *Acta physiol. scand., Suppl.*, **83**, 1.
——, and JASPER, H. (1952) *Arch. Neurol. Psychiat., Chicago*, **68**, 609.
KLÜVER, H., and BUCY, P. C. (1939) *Arch. Neurol. Psychiat., Chicago*, **42**, 979.
LIBERSON, W. T., SCOVILLE, W. B., and DUNSMORE, R. H. (1950) *Proc. Am. EEG Soc.*, fourth annual meeting, June, 1950.
——, SCOVILLE, W. B., and DUNSMORE, R. H. (1951) *Electroenceph. clin. Neurophysiol.*, **3**, 1.
——, HENRY, C., SCOVILLE, W. B., and DUNSMORE, R. H., *Anatomo-physiol. céréb. Biol.*, **3**, 205.
——, and CADILHAC, J. C. (1953) *Proc. Amer. Psychiat. Ass.*, meeting at Los Angeles, May, 1953.
——, and AKERT, K. (1955) *Electroenceph. clin. Neurophysiol.*, **7**, 211.
LORENTE DE NÓ, R. (1933) *J. Psychol. Neurol., Lpz.*, **45**, 381.
—— (1934) *J. Psychol. Neurol., Lpz.*, **46**, 113.
LOTHEISSEN, G. (1894) *Anat. Hefte*, **4**, 225.
MACLEAN, P. D., HORWITZ, N. H., and ROBINSON, F. (1952) *Yale J. Biol. Med.*, **25**, 159.

MISHKIN, M. (1954) *J. comp. physiol. Psychol.*, **47**, 187.
——, and HALL, M. (1955) *J. comp. physiol. Psychol.*, **48**, 97.
——, and PRIBRAM, K. H. (1954) *J. comp. physiol. Psychol.*, **47**, 14.
MORIN, F. (1950) *J. comp. Neurol.*, **92**, 193.
MORUZZI, G., and MAGOUN, H. W. (1949) *Electroenceph. clin. Neurophysiol.*, **1**, 455.
PENFIELD, W. (1954) *Brit. med. J.*, **2**, 1159.
POWELL, T. P. S., and COWAN, W. M. (1954) *J. Anat., Lond.*, **88**, 489.
——, —— (1955) *Brain*, **78**, 115.
PRIBRAM, K. H., and MISHKIN, M. (1955) *J. comp. physiol. Psychol.*, **48**, 198.
RAMÓN Y CAJAL, S. (1911) "Histologie du système nerveux de l'homme et des vertébrés." Paris, Vol. 2.
RENSHAW, B., FORBES, A., and MORISON, B. R. (1940) *J. Neurophysiol.*, **3**, 74.
SCHREINER, L., and KLING, A. (1953) *J. Neurophysiol.*, **16**, 643.
SCOVILLE, W. B., DUNSMORE, R. H., LIBERSON, W. T., HENRY, C. E., and PEPE, A. (1953) *Res. Publ. Ass. nerv. ment. Dis.*, **31**, 347.
SIMPSON, D. A. (1952) *J. Neurol. Neurosurg. Psychiat.*, **15**, 79.
SPRAGUE, J. M., and MEYER, M. (1950) *J. Anat., Lond.*, **84**, 354.
TUNTURI, A. R. (1944) *Amer. J. Physiol.*, **141**, 397.
—— (1950*a*) *Amer. J. Physiol.*, **160**, 395.
—— (1950*b*) *Amer. J. Physiol.*, **162**, 489.
WOOLSEY, C. N., and WALZL, E. M. (1942) *Bull. Johns Hopk. Hosp.*, **71**, 315.

LEGENDS TO PLATES

PLATE XXXV

FIG. 4.—Phalanger S5. Evoked potentials recorded bipolarly in 2 mm. steps across the auditory cortex in response to click stimulation 144 days after entorhinal ablation. Each cathode-ray trace corresponds in its position in the map to the placement of the bipolar recording electrodes indicated on the brain-figure at the right. In each case the early large deflection occurring approximately 50 msec. from the start of the trace is the primary cortical response. In the central part of the responsive area the initial waves of the spindle trains can be seen beginning about 300 msec. after the primary response. By contrast the rapid background activity anteroinferiorly is not significantly modified following the primary cortical response. Curarized preparation.

PLATE XXXVI

FIG. 5.—Simultaneous records from the auditory cortex (C) and the hippocampal formation (H) 33 days after bilateral entorhinal ablation. Records A and B, click stimuli; records C and D, hand claps. Successive stimuli delivered approximately 30 seconds apart to form a single series A, B, C, D. In each record there is a large primary evoked hippocampal response. The ensuing slow-wave train, well marked in A, gradually diminishes in the following records. Curarized preparation.

PLATE XXXVII

FIG. 6.—Records from somatic area II, recorded bipolarly, of responses to auditory and somatic stimulation. In each of the series of combined stimulations, auditory stimulation precedes the somatic. Auditory stimulus, click; somatic stimulus, shock to ipsilateral forepaw. Curarized preparation.

PLATE XXXV

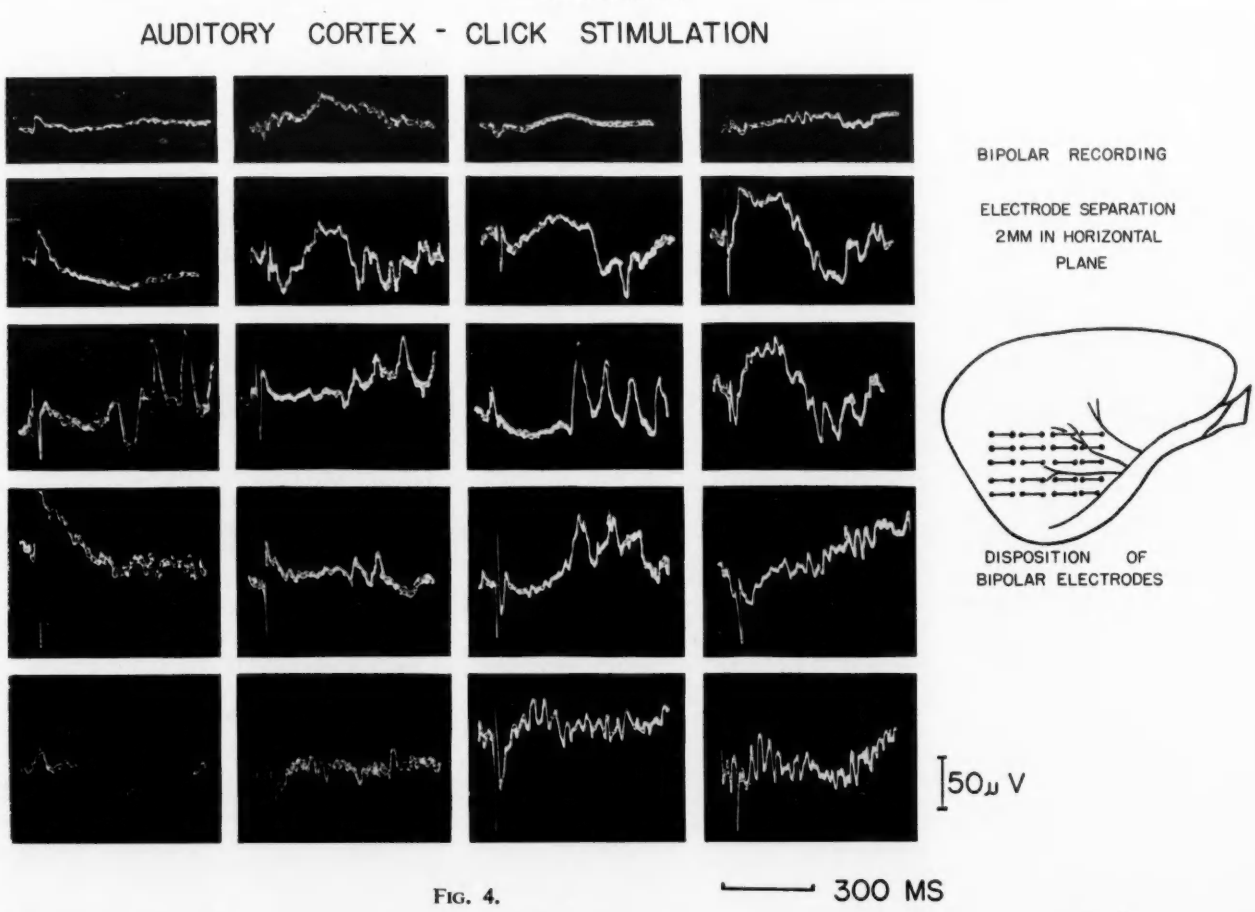

FIG. 4.

To illustrate article by W. R. Adey, N. C. R. Merrillees and S. Sunderland.

PLATE XXXVI

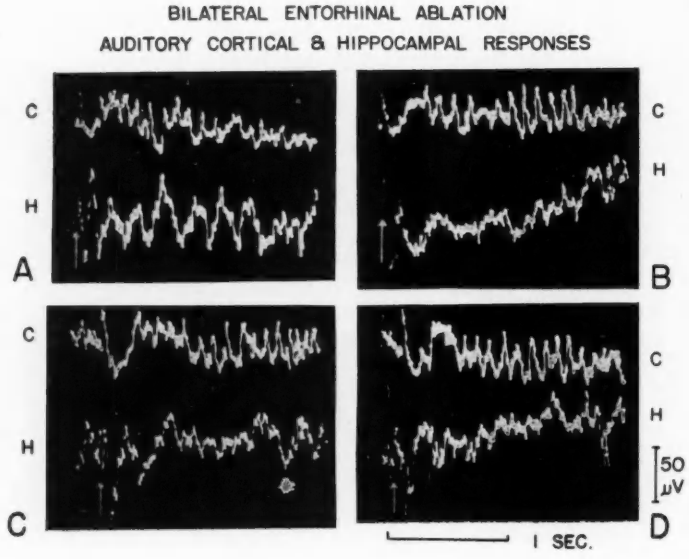

FIG. 5.

To illustrate article by W. R. Adey, N. C. R. Merrillees and S. Sunderland.

PLATE XXXVII

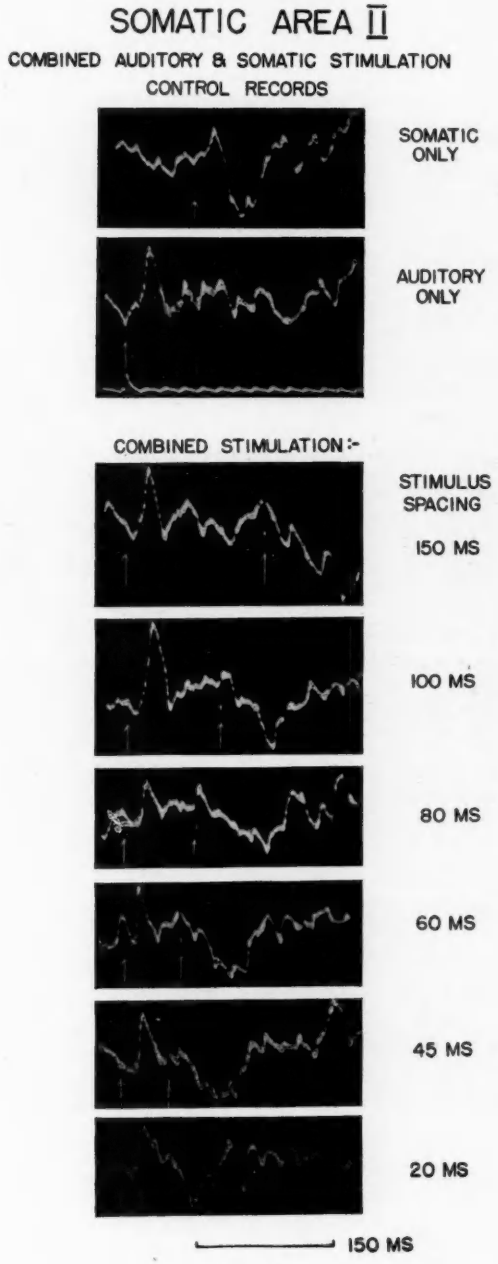

FIG. 6.

To illustrate article by W. R. Adey, N. C. R. Merrillees and S. Sunderland.

PLATE XXXVIII

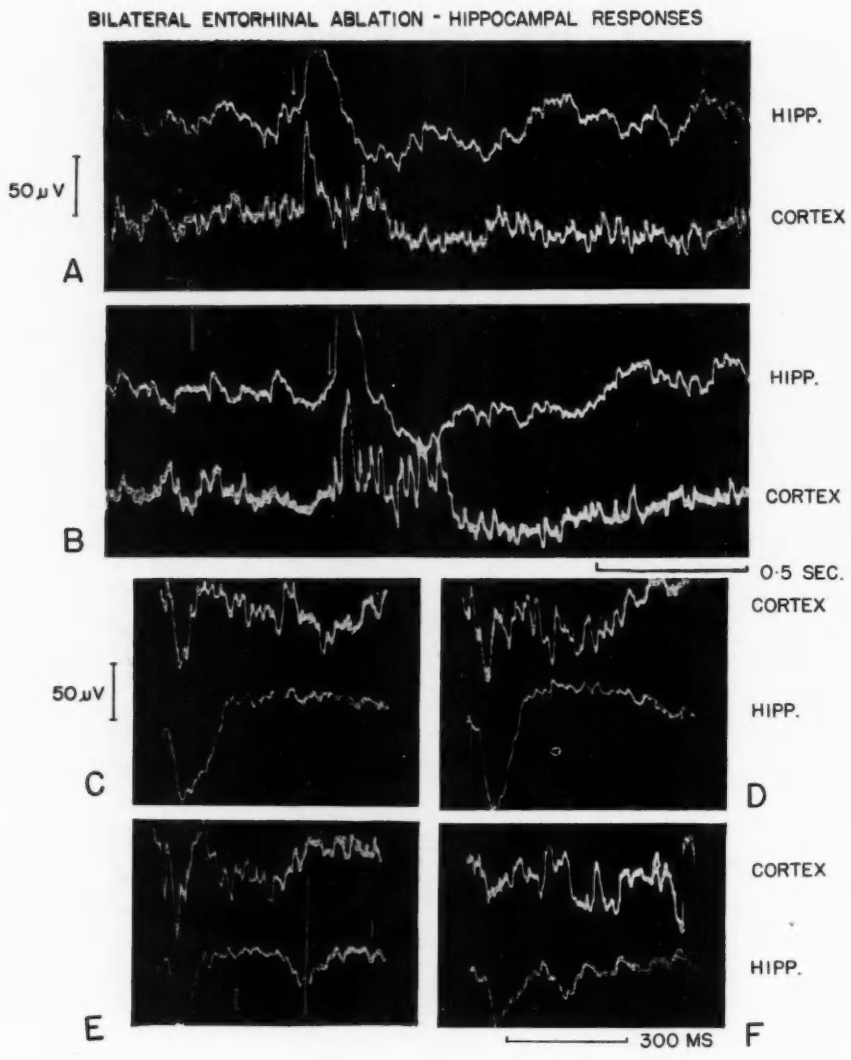

FIG. 7.

To illustrate article by W. R. Adey, N. C. R. Merrillees and S. Sunderland.

PLATE XXXIX

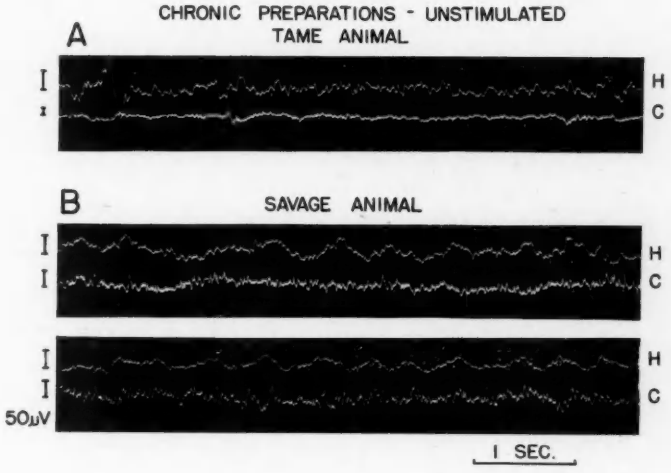

FIG. 8.

To illustrate article by W. R. Adey, N. C. R. Merrillees and S. Sunderland.

PLATE XL

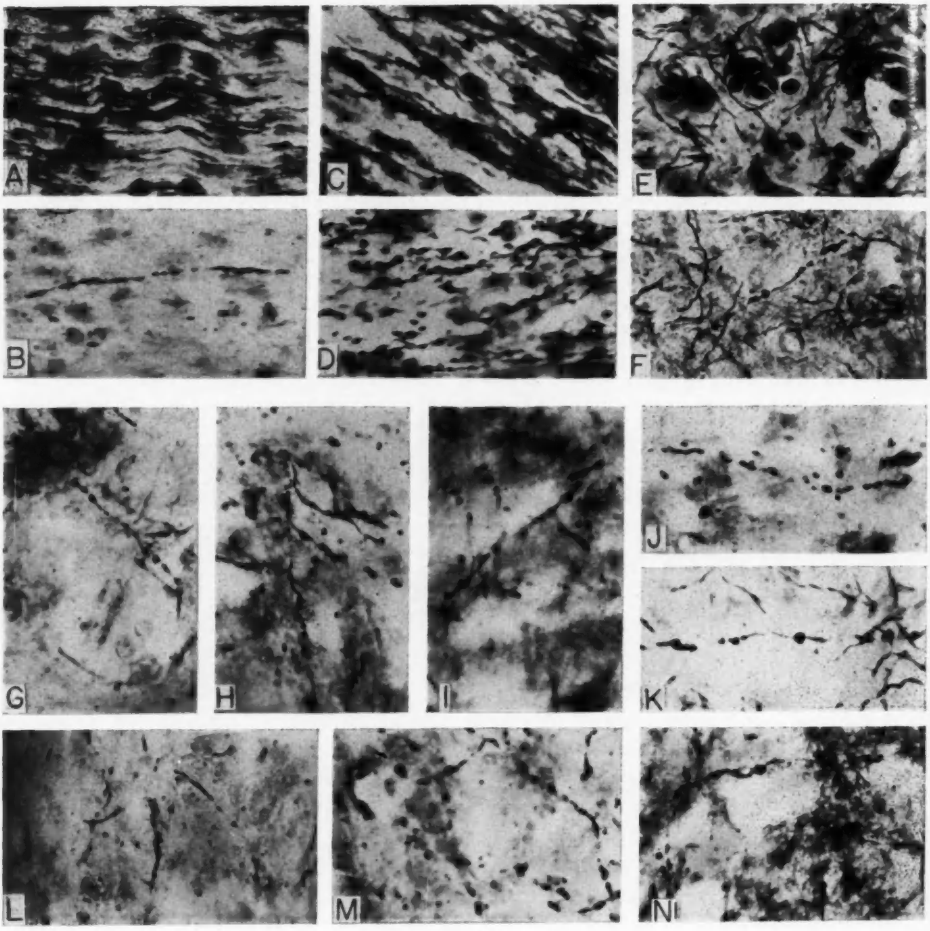

FIG. 10.

To illustrate article by W. R. Adey, N. C. R. Merrillees and S. Sunderland.

PLATE XLI

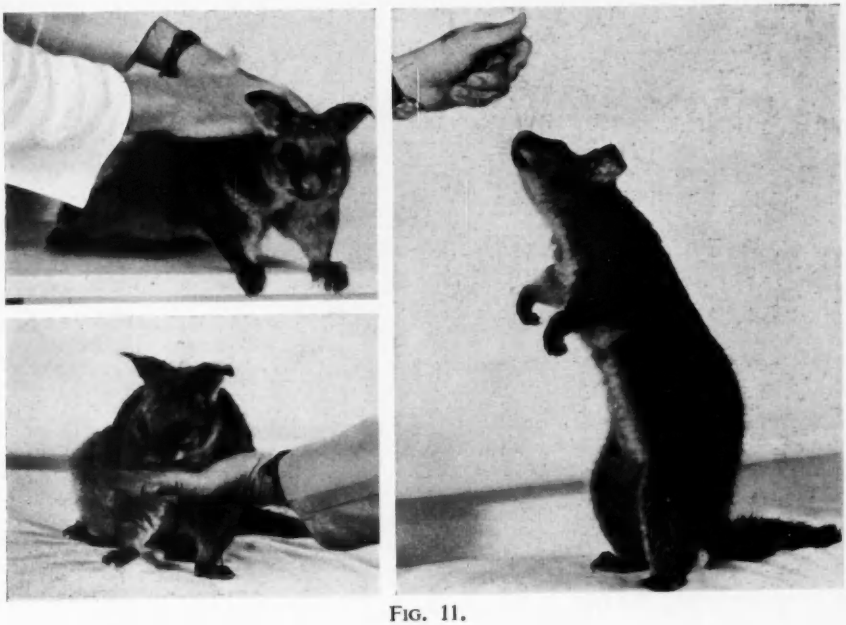

FIG. 11.

To illustrate article by W. R. Adey, N. C. R. Merrillees and S. Sunderland.

PLATE XXXVIII

FIG. 7.—Simultaneous cortical and hippocampal records of responses to click stimulation seven days after bilateral entorhinal ablation. Moment of stimulation indicated by arrows in tracings A and B. Stimulus delayed 15 msec. after start of trace C, D, E and F. Curarized preparation.

PLATE XXXIX

FIG. 8.—Simultaneous cortical and hippocampal records of spontaneous activity in chronic experiments. Tame animal, phalanger S9; savage animal, phalanger S8. The long trains of hippocampal slow-waves in the savage animal are in marked contrast to the irregular activity in the tame preparation. Both records obtained under curare.

PLATE XL

FIG. 10.—Microscopic appearances in normal and operated material stained by the Nauta method. It may be emphasized that in the normal material (A, C and E) every effort has been made to display maximum fibre detail in these photographic reproductions, but that by this method normal tissue displays little argentophilia. Thus to the eye the fibres in the normal material would appear as a pale background similar to that shown in the degenerating preparations.

A: normal anterior commissure. × 900.

B: phalanger S2. Degenerating fibre in the anterior commissure. × 900.

C: stria medullaris in normal material. × 900.

D: phalanger S7. Degenerating fibres in the stria medullaris. × 900.

E: normal mid-brain tegmentum at the level of the superior colliculus. × 900.

F: phalanger S4. Degenerating terminal amongst cells of the mid-brain tegmentum on the same side as the lesion at the level of the superior colliculus. × 1,100.

G: phalanger S4. Degenerating terminal amongst cells of the periventricular grey matter at the level of the superior colliculus on the side opposite to lesion. × 1,200.

H, I, J: phalanger S4. Fibre and terminal degeneration in mid-brain tegmentum on the same side as the lesion. × 1,200.

K: phalanger S4. Fibre degeneration at the level of the superior colliculus in the outer part of the periventricular grey matter on the same side as the lesion. × 1,500.

L, M, N: phalanger S4. Fibre and terminal degeneration amongst tegmental cells at the level of the inferior colliculus on the same side as the lesion. × 1,200.

PLATE XLI

FIG. 11.—Phalanger S3. Fifteen days after bilateral entorhinal ablation, showing characteristic post-operative curiosity and tameness,

A NEUROLOGICAL APPRAISAL OF FAMILIAL CONGENITAL WORD-BLINDNESS

BY

ARTHUR L. DREW

(*From Department of Neurology, University of Michigan, Ann Arbor, Michigan, U.S.A.*[1])

Familial Dyslexia

Reading disabilities, unless associated with obvious and gross cerebral damage, have come to be regarded as psychological or pedagogical problems apparently unrelated to the functions of the central nervous system. Most writers on the subject have concluded that there is no evidence of organic neurological dysfunction in cases of reading disability.

However, since 1905 (Fisher, Thomas) many case reports in the literature have suggested a genetic factor in some forms of dyslexia. Hallgren (1950), on the basis of an analysis of 116 cases of dyslexia, was able to conclude that:

"The genetic statistical analysis shows that specific dyslexia with a high degree of probability, follows a monohybrid autosomal dominant mode of inheritance."

Thus a single gene is involved in a dominant non-sexlinked form of inheritance. Hallgren's work (1950) is the most complete study yet available and tends to confirm the conclusion of earlier workers who made less complete investigations but who for the most part suspected a dominant genetic tendency.

If dyslexia is inherited as a dominant trait then either there is a "pure word-letter-blindness" due to failure of formation or maturation of a "reading centre"; or "pure word-letter-blindness" does not exist, and in inherited dyslexia other associated neurological abnormalities can be expected if properly searched for and assessed. The first alternative requires a return to the now generally outmoded concept of discrete cerebral localization of function. On the other hand, if associated neurological abnormalities are detected in genetically determined dyslexias, it is necessary to attempt to postulate a unitary defect of cerebral function, which is capable of dominant genetic transmission. Any such formulation must be able to incorporate the many apparently diverse observations into

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an organic whole compatible with the corpus of neurological knowledge. Such a theory can ignore neither the anatomical nor physiological facts of cortical localization, nor can it ignore the psychological aspects of dyslexia. In reference to familial dyslexia any acceptable hypothesis should also permit the postulation of a unitary defect capable of dominant genetic transmission.

It is the purpose of the present paper to examine the above proposition by a review of the literature and by the analysis of an instance of familial dyslexia which has been studied personally. Three instances of reading disability occurring in a single family are presented as examples of familial dyslexia. It is believed that by the analysis of this material a clearer concept of the nature of hereditary dyslexia may be arrived at.

Case Material

C. W., a 16-year-old boy, was seen in the clinic because of headache. In the course of investigation of this complaint a history of severe difficulty in reading was elicited. The patient as well as his father and his half-brother (by the father) were investigated as possible examples of congenital hereditary dyslexia.

The family history revealed that the patient's father, A. W., and a half-brother, B. W., both had reading disabilities. The paternal grandfather was also said to have been a non-reader although his mother was a school-teacher and his education was chiefly at her hands. A 6-year-old girl, one of twins, the daughter of B. W., was thought by her father and grandfather to have a similar difficulty in learning to read. A family history involving several generations was obtained. With the exception of multiple marriages and one paternal relative in a state hospital for the insane, nothing else of note was detected in the family history. Details concerning speech defects and handedness were not obtained other than the report of the father that he could remember no one in the family who was left-handed or who had "trouble talking."

The patient's father, A. W., was a successful farmer who reported an income of over $400 a month and owned his own farm. He stated that he took care of all the financial matters, doing his own accounts, but that his wife always read contracts and other business papers to him. He was educated in country schools, moving from school to school as a child. In retrospect this 48-year-old man believed that he had no trouble in school except with his reading. He eventually completed the eighth grade.

The older son (B. W.), aged 23, also completed the eighth grade and reported great difficulty with reading. Since his marriage his "wife has taught him to read" although he still was "not a reader," according to his own view. This boy and the younger patient (C. W.) were children of the father (A. W.) by separate marriages. The first marriage was not a

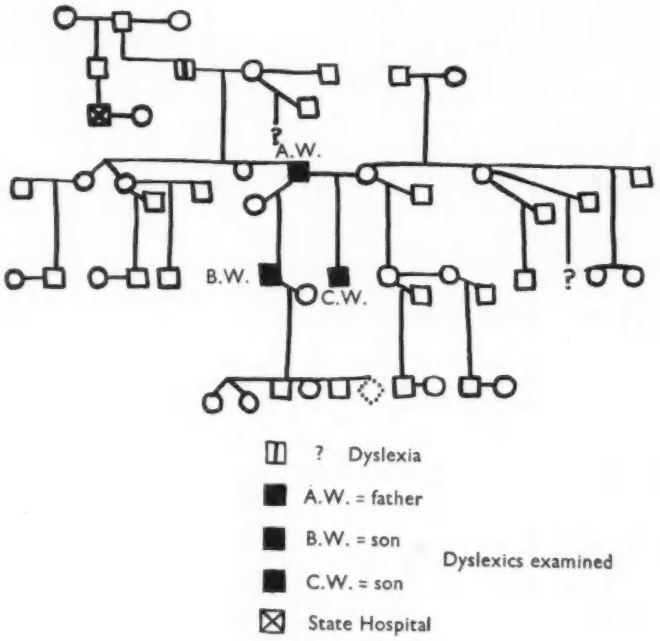

FIG. 1.

happy one and the wife and B. W. had no contact with the father (A. W.) until three and a half years ago. B. W. stated that he had attended "at least 20 schools" finally completing the eighth grade in a rural school. He was married, with 5 children, and worked as a machinist. His birth and neonatal development were uneventful according to the father but neither B. W. nor his father could give any detail concerning infantile illness or trauma. The patient recalled no illness or injuries at any time.

The younger son (C. W.), aged 16, is also reported to have had an uneventful birth and early developmental period, walking at 11 months and talking at 22 months. No history of trauma or severe illness was elicited except for his presenting complaint of dull headache which had first occurred a year before, lasting for several months and recurring five months before his entrance to the clinic. This headache had all the features of a "tension headache." A psychiatric consultant concurred in this opinion, believing the symptom to be secondary to "adolescent problems of motivation" and the reading disability.

This patient was in the fifth grade of a District School at the time of this examination. His parents stated his marks were "fair" to "good" in all

subjects except reading. He had received "special tutoring" in reading for the two months prior to the present examination.

All 3 patients were given the Durell Reading Test. The results are given in Table I.

TABLE I

	A. W.	*B. W.*	*C. W.*
Reading Rating 4/72=1st grade	4th–5th grade	5th–6th grade	37/72
Spelling 2/10=2nd grade	5/10	1/10	8/10
Copying 0–3/35=2nd grade	3/29	10/101	8/32
Reversals (x)	0	0	1
Omissions and Confusions (y)	1	0	9
Total on Durell Reading Readiness Test (x+y)	1	0	10

The Wechsler-Bellvue Intelligence Scale, Form I[1] was administered to the two sons (B. W. and C. W.). Unfortunately the father (A. W.) was not tested. The results are given in tabular form in Table II, and a "psychograph" of both patients is shown in Table III.

A general physical examination was performed on all 3 patients. No abnormalities were found and no systemic complaints were elicited. A detailed neurological history revealed only the complaint of headache in one son (C. W.) and intermittent low back pain in the other (B. W.).

The neurological examination will be given in considerable detail for the father including both abnormal and normal findings. The examinations of the two sons will be reported in terms of abnormal findings alone. In so far as is ever possible, the 3 patients were subjected to identical examinations.

Case I.—A. W. (father—aged 48). The patient was co-operative and interested in the examination. He was at ease and showed no evidences of anxiety, fatigue or abnormalities in affective tone at any time except for some embarrassment at his poor performance in some parts of the aphasia testing.

The gait could be considered non-specifically awkward and clumsy but when allowances are made for a lifetime of manual farm labour, it was perhaps not abnormal. The associated movements of arms and legs were normal. No ataxia, uncertainty or asymmetry of weight bearing was present. The Romberg test was entirely normal.

There were no asymmetries of the skull, face or extremities. Muscle bulk and strength were excellent and entirely symmetrical. The palms were equally calloused and showed evidence of much manual labour.

He showed a distinct preference for the left eye, the right hand and the right foot on several separate tests as well as on observation throughout several hours of examination.

Finger to nose, finger to finger, and heel to knee tests were well performed. Check, rebound and tests for past-pointing were normal. There was no abnormal posturing

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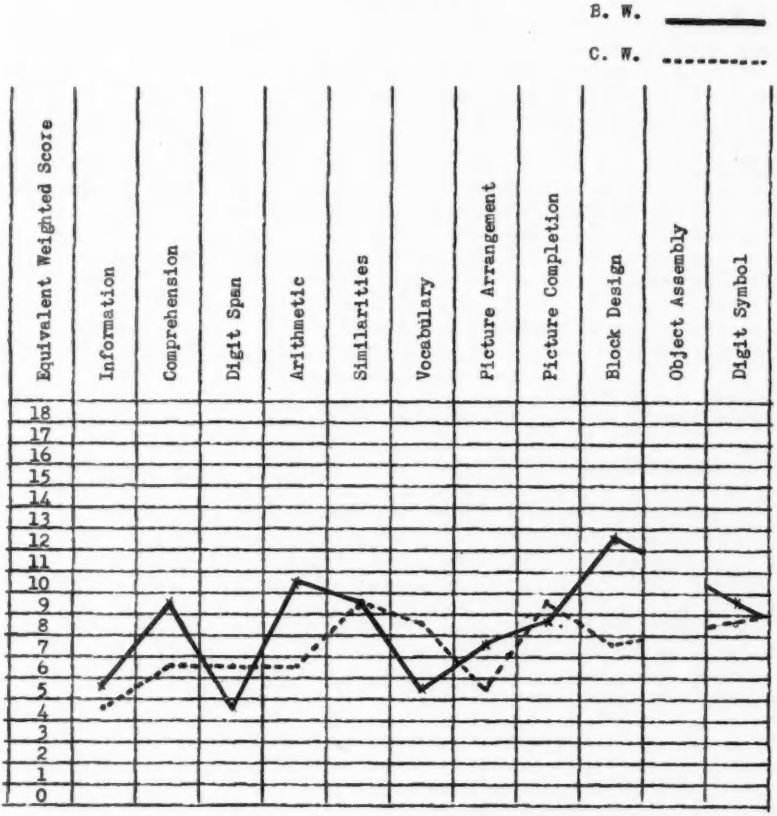
TABLE II.—WECHSLER-BELLVUE INTELLIGENCE SCALE

	B. W.	*C. W.*
Information	6	5
Raw Score	6	5
Weighted Score	5	4
Comprehension		
Raw Score	10	7
Weighted Score	9	6
Digit Span		
Raw Score	8	9
Weighted Score	4	6
Arithmetic		
Raw Score	8	5
Weighted Score	10	6
Similarities		
Raw Score	11	11
Weighted Score	9	9
Vocabulary		
Raw Score	10	17
Weighted Score	5	8
Picture Arrangement		
Raw Score	8	5
Weighted Score	7	5
Picture Completion		
Raw Score	9	10
Weighted Score	8	9
Block Design		
Raw Score	25	14
Weighted Score	12	7
Object Assembly (omitted)		
Digit Symbol		
Raw Score	40	34
Weighted Score	9	8
Verbal Scale		
Pro rated	35	33
I.Q.	85	83
Performance Scale		
Pro rated	45	36
I.Q.	92	80
Full Scale		
Pro rated	80	69
I.Q.	87	80

of head, neck or extremities. There were no abnormal involuntary movements or any evidence of pseudo-athetosis or drifting of the outstretched hands. Rapid succession movements of both upper and lower extremities were synchronous bilaterally and co-ordinated but in testing rapid successive movements of the fingers there was some slowing and the examiner gained an impression of clumsiness. This may or may not have been related to the background of heavy manual labour.

Examination of the superficial reflexes was negative. The deep tendon reflexes were consistently slightly more active on the entire right side. There was an asymmetrical

TABLE III



plantar response. Flexion of the great toe with fanning of the other toes was observed on the right side. The response of the left was unequivocally normal. This was a reproducible response.

The first cranial nerve was normal. Visual acuity as tested with a Snellen "E" chart was 20/30 bilaterally without correction. Visual fields were tested by simultaneous binocular confrontation as well as routine monocular confrontation and no abnormalities of the visual fields were found by these methods.

Ocular movements, pupillary form and reactions were normal. The fifth, seventh, eighth, ninth, tenth, eleventh and twelfth cranial nerves were entirely normal. His speech can perhaps best be characterized as "bucolic." No cluttering, distortions or condensations were detected either on test phrases or during the rest of the examination. His auditory comprehension appeared in no way abnormal, as judged by his response to the complex instructions given during the examination or by direct testing with similarly sounding words or easily confused sentences.

He showed no abnormalities in routine testing of pain, touch, hot, cold, vibratory, position and motion, or deep pain sensations.

There was definite delay in appreciation of simultaneous homolateral face-hand stimulation (10 trials, right face and hand; 12 trials, left face and hand). No other extinction (inattention) phenomena were found. No allæsthesia was found. There was no astereognosis or simultaneous astereognosis. No graphanæsthesia was found. Two point tactile discrimination was slightly impaired but bilaterally equal. This may well have been a result of heavily calloused hands.

There was no finger agnosia and no laterality confusion on Head's hand-eye-ear tests (Head, 1926).

The patient was asked to identify by name a penny, spoon, matchbox, comb, pencil and key which were shown to him. This was done without error or hesitation. He identified each object on oral command. When asked to match the printed name of the object with the actual object he missed "spoon" and was very unsure with "comb." Copying the printed word into script was performed accurately except for one error—he wrote "penciil."

Writing the name of the object shown: When shown a penny—"I can't write that name, but I can write 'cent'," which was done correctly. "Spoon" was done well. "Key was started with an "H" and then crossed out and written correctly. Comb was "comp." When shown the matchbox, the patient turned it over and smiled at seeing the label "Matches" and then proceeded to write "Matches-box."

He was able to write only "p" for penny and failed with all the other words when trying to write from dictation.

The patient recognized all printed and written letters of the alphabet when presented out of sequence.

He recognized all numbers 1 to 10 as well as three- and four-digit numbers.

There was no impairment of colour-naming or discrimination.

He was able to draw a "blueprint" of his house (said to be accurate by the wife) which showed great care and was frequently corrected during its execution. He copied a picture of a boat, fairly accurate in all detail, but with no attempt to show perspective. He was able to reproduce this drawing in fifteen minutes without having been forewarned of the latter part of the test.

He was able to perform Head's man-cat-dog test (Head, 1926) of reading from pictures.

Case II.—B. W., the 23-year-old son, showed no abnormalities on a neurological examination embodying all the features given in detail for his father (A. W.). He was right-eyed, right-footed and right-handed. Analysis of the Wechsler-Bellvue test items showed a very poor vocabulary, constant reversal of И to N and almost uniform rounding off of] to) in the Digit-Symbol test.

Scrutiny of the Block Design test was also interesting. He first confused yellow with white and corrected himself. Two other designs were built with 30 and 45 degree rotations respectively.

The Bender-Gestalt test was interpreted as showing "organicity" with some regressive features and the question of deterioration was raised. However, nothing that could be considered gross disturbance was seen. Some failure to "close" the figures was seen but otherwise the "gestalten" were not severely distorted.

In writing from dictation he writes "Kee" for "Key" and "Pincil" for "pencil." "Penny" is started as "peny" and corrected. The rest of the aphasia tests were performed without error or appreciable distortion.

Case III.—C. W., the youngest son (aged 16) who is virtually a non-reader, had the most abnormal examination of any of the 3 patients.

The positive findings included a slight inequality of deep tendon reflexes, the right-sided reflexes being slightly increased. There was, as in the father, a normal plantar

reflex on the left, but on the right, fanning of the toes and incomplete flexion of the great toe was again observed. These findings were reported independently by two separate examiners. The similarity of the reflex picture in the father was startling.

This boy was right-eyed, right-footed and right-handed. There was confusion of laterality only when seated opposite the examiner and attempting to copy Head's hand-eye-ear tests. Here there was considerable confusion and failure to correct errors which involved crossing the mid-line. He also made many errors in graph-æsthesia testing with both letters and figures. Both hands appeared equally involved. There was a very marked delay in simultaneous stimulation of face and hand either unilateral or crossed. No other extinction or inattention phenomena were noted.

The aphasia test was most abnormal. He was able to name all the objects shown and identify them by oral command. He was totally unable to match the object with the printed (or written) name. He could not write anything from dictation except "Cen" for "key." His attempts to write the name of the object indicated to him and his attempts to copy are shown in fig. 2.

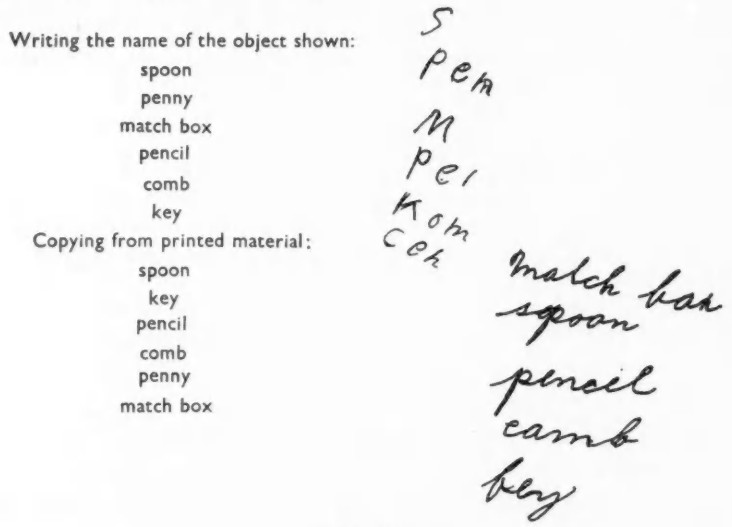


FIG. 2.

He recognized the alphabet in both capital and small letters (print and script).

He correctly named and matched red, green, black, blue and yellow but in the Block Design test he showed marked confusion between yellow and white, even when corrected.

He was able to reproduce the boat drawing in good detail after a twenty-minute interval.

The floor plan, although correct in detail, showed the furniture completely out of scale with the room, according to the father, who was asked to comment. In addition the furniture was drawn as though it occupied only the periphery of a very large room. This was inaccurate according to the father.

Study of the individual test items of the Wechsler-Bellvue scale revealed errors in the Digit-Symbol and Block Design tests which were very like those noted in his elder

brother's protocol. C. W. habitually wrote И for N and in the Block Design test had trouble with yellow-white distinctions and also rotated two figures.

During the neurological and aphasia examinations no defects in attention or auditory comprehension were noted. However, during the psychological testing the examiner commented that the patient "does not attend, if you give him instructions without first attracting his attention, he waits until you are finished and asks—'what did you say'."

There was evidence of immaturity in the Bender-Gestalt but no other disturbance was noted. Comparison of the test results here left little question that there was more disturbance expressed in the older patient's (B. W.) record than in the younger boy's drawings despite the fact that C. W. had by far the most severe reading disability.

Electroencephalographic records on the two boys (B. W. and C. W.) were obtained. The record in the case of the older boy showed some borderline disturbances consisting of episodic high voltage diphasic discharges occurring in the post-sagittal region, but elsewhere as well. There was no focal abnormality or any lateral emphasis.

The younger son's (C. W.) record showed some mixed abortive 4 or 5 per second generalized bursts both with and without spike-wave formation. Again no focal or lateralized disturbance was noted, and the record was interpreted as being abnormal and paroxysmal with probable lower level trigger mechanism.

Discussion

Morgan (1896) and Kerr (1897) are credited by Hinshelwood (1917) with suggesting the concept of congenital dyslexia as a clinical entity and with reporting the earliest cases of congenital word-blindness. "Word-blindness" is the term coined by Kussmaul in 1877, although Lordat (Riese, 1954) had very vividly described his own inability to read as early as 1843. The various aspects of acquired or secondary dyslexias and alexias have received a great deal of attention in neurological literature over the years. Nielsen (1946) defined alexia as "loss of ability to read without reference to the physiological cause except that it is due to a focal cerebral lesion. Sufficient visual perception and mental capacity are presupposed." The same author lists some twelve types of alexia due to focal lesions ranging from frontal to occipital poles. Critchley (1953) after reviewing the subject suggests that acquired reading disabilities may be best viewed as "representing either a partial affection of language or else a fragment, or residuum of a visual agnosia."

The aphasic and agnostic forms of dyslexia and alexia are familiar to the neurologist in many forms, in association with a wide variety of symptoms caused by lesions involving the parietal and occipital lobes, whatever may be the precise psychological, anatomical or physiological hypothesis used to explain the relation between structure and function.

We are not, at the moment, concerned with these acquired or secondary forms of "word-blindness." There is general acceptance of the fact that acquired cerebral lesions may result in various agnostic and aphasic disturbances of the ability to perceive and comprehend visual verbal material. It has also been urged that "pure" alexia on either an agnostic or aphasic basis is probably a misnomer and that "either dyslexia is

found on appropriate testing to be an incomplete defect and an inconstant one, or else other aspects of speech are demonstrable in alleged cases of pure reading disability" (Critchley, 1953).

It is in part the purpose of the present paper to examine the proposition that a similar criticism may be levelled at the concept of "pure congenital word-blindness." "Congenital word-blindness" as a clinical entity was first introduced by Morgan (1896). Since that time a great many descriptive terms have been suggested. Among these are congenital word-blindness (Morgan, 1896), strephosymbolia (Orton, 1928), specific dyslexia (Hallgren, 1950), constitutional dyslexia (Skydsgaard, 1942), congenital symbol-amblyopia (Claiborne, 1906), congenital typholexia (Variot and Lecomte, 1906), specific reading disability (Bender and Schilder, 1951), congenital alexia (Stephenson, 1907), developmental alexia (Jackson, 1944; Orton, 1937; Chance, 1913), bradylexia (Claparède, 1917), analfabetia partialis (Wolff, 1916), amnesia visualis verbalis (Witmer, 1907), congenital dyslexia (Rutherfurd, 1909), primary reading retardation (Rabinovitch, Drew *et al.*, 1955).

All of these terms tend to refer to cases of reading disabilities which occur congenitally as a highly selective fault without recognizable ætiology and in which the dyslexic symptom is said to be unassociated with other aphasic or agnostic elements. In fact it is claimed that no evidence of neurological involvement can be found in these patients.

A perusal of much of the literature fails to lead to any clear conception of congenital word-blindness as a clinical entity. Difficulty in reading may result from many causes. Monroe (1932) was able to list fifteen general groups of "causative factors in reading disability." However, since 1896, the literature continues to contain references to a form of congenital reading disturbance which cannot be ascribed to "poor intelligence, intellectual and physical immaturity, emotional factors, defects of sense organs, disturbances of articulations and other motor functions, reduced physical vitality, home and school conditions, dialect and other lingual difficulties" (Skydsgaard, 1942).

There is great variability in the estimates of the incidence of congenital dyslexia and this is a fair gauge of the inconstancy of definition of the condition. These estimates range from 0·02 per cent (Bachmann, 1927) to 10 per cent (Hallgren, 1950; Bakwin and Bakwin, 1948) and as high as 20 per cent (Preston, 1940). At the present time, if there are accurate diagnostic methods, these methods are not sufficiently standardized or in use to permit of any entirely valid estimate of the incidence of true congenital dyslexia. Both the tendency to overdiagnose and the failure to diagnose invalidate most, if not all, estimates of the true incidence and in addition contribute materially to the confusion of definition of the entity.

Particularly in the earlier case reports, congenital syphilis, cerebral palsy or other causes of acquired dyslexia have been included.

The diagnosis of congenital dyslexia presents many difficulties. There is no unanimity of opinion regarding diagnostic criteria. Blau (1946) recommends that if a child is two years retarded in reading ability as compared to mental age, a diagnosis of reading disability be made. Others have worked out elaborate formulæ for detecting congenital dyslexia (Monroe, 1932; Skydsgaard, 1942; Rønne, 1936). The majority of writers have contented themselves with less rigid diagnostic criteria and to some extent their estimates of incidence and other conclusions are thereby open to criticism. Hallgren (1950) and Launay (1952) urge essentially pedagogical definitions as did Orton (1937).

Rabinovitch, Drew *et al.* (1955) have suggested that the diagnosis of reading retardation be made in those children whose reading ability, as tested by any standard reading test, is two years below the mental age determined by the performance portion of a standard intelligence test. The distinction between primary reading retardation (congenital dyslexia) and secondary reading retardation due to a whole host of exogenous factors must be made on other grounds.

It is little wonder that some authors tend to deny the existence of specific dyslexia (Burt, 1935; Gates, 1927; Witty and Kopel, 1939) while others regard congenital word-blindness as simply an individual variant at the lower end of a curve representing the reading skill of the normal population (Meyer *et al.*, 1943; Larsen, 1947). Still others urge a multifactorial origin of reading disabilities (de Ajuriaguerra, 1951; Monroe, 1932 and others) which is simply a compromise which basically refutes the existence of congenital dyslexia as an entity.

Some have chosen to define congenital word-blindness as simply a symptom of more basic phenomena, e.g., defective intelligence (Berkhan, 1917; Laubenthal, 1936, 1938). However, the association of dyslexia with superior or normal intelligence as well as inferior or defective intelligence has been well documented in many studies (Orton, 1925; Eustis, 1947*b*; Fildes, 1921; McCready, 1926; Hallgren, 1950; Skydsgaard, 1942).

Many (Stewart, 1950; Laubenthal, 1936, 1941; Gann, 1945; Ellis, 1949; Blanchard, 1946; Pearson, 1952) have emphasized emotional factors as basic in the ætiology of reading disorders and Blau (1946) takes the position that "the language disturbance is secondary and only one of the many symptoms of the personality disorder" which is "a negativistic type of emotional disturbance."

However, Blanchard (1946) suggests that only about 20 per cent of reading disabilities are "of a neurotic type amenable to psychotherapy" and Gates (1941) believes that only in some 25 per cent is personality maladjustment the basis of the reading disturbance. Pearson (1952) has "felt it necessary to re-emphasize it (the organic) because at the present

time when there is so much emphasis on the importance of intrapsychic processes in all phases of medicine and education, psychiatrists tend to become over-enthusiastic about dynamic intrapsychic processes to the complete neglect of physiological and organic processes, for which they seem to have a psychic blind-spot."

"Children with reading disabilities certainly have personality problems and neurotic reactions. There appear, however, to be few common factors except a relative immaturity and a need to build up some defence mechanisms or compensation" (Bender and Schilder, 1951). McCready (1926), Orton (1937), Hallgren (1950), Skydsgaard (1942) and Bakwin and Bakwin (1948) among others are also of the opinion that behaviour disorders, personality problems and emotional disturbances are in general secondary and the result of the reading disability.

The close association of a background of general physical illness, or the presence of chronic medical and surgical disease (exclusive of neurologic disease) and congenital dyslexia, has been stressed by some (Jackson, 1944; Eames, 1935) and denied by others (Anderson and Kelly, 1931). In fact, Anderson and Kelly (1931) could not show a higher instance of birth injury, head injuries and neurological disease in reading disability cases as compared to a control group.

Other investigators have urged the definition of reading disabilities in terms of their hypotheses covering the ætiology of the disability. Thus, such environmental factors as frequent physical (non-neurological) illness, inadequate or theoretically improper teaching (look-say versus phonetic methods), and frequent school changes have all been implicated in the ætiology and the definition of reading disability (Hallgren, 1950; Skydsgaard, 1942; Hirsch, 1952). It is difficult to explain away the genetic forms of reading disability on these grounds.

It also seems unlikely that congenital dyslexia defined in terms of single associated findings will be readily acceptable to most workers in the field. Thus reversals in reading and writing, left-handedness, mixed hand-eye-foot patterns and peripheral visual and auditory abnormalities have all at one time or another been considered the determining factor, the essence of congenital dyslexia. Innumerable statistical studies have been brought forward refuting the claim of each single factor. The studies of Johnston (1942), Jones (1944), Drews (1954), Monroe (1932), Witty and Kopel (1936*a* and *b*) and Irvine (1941) fail to find such factors significant correlates of congenital dyslexia.

It is believed that the father and younger son reported here represent true cases of familial dyslexia. Judging by errors in the aphasia test, historical evidence of reading difficulty, and some residual disturbances in the Wechsler-Bellvue tests, the older son is believed to be a case of familial dyslexia which had been partially corrected by exogenous influence, and perhaps by maturation. Perhaps this patient illustrates, to some extent,

Yacorzynski's (1949) thesis that learning and perception are different but functionally related mechanisms, mediated through different parts of the nervous system, yet capable of affecting each other by changes in either alone.

In view of the neurological abnormalities, detectable in a routine examination, it appears that the oft-repeated statement that no neurological abnormalities co-exist with familial congenital dyslexia is an error, at least in so far as the present material is concerned. In fact, cases presented by Eustis (1947), Launay and Borel-Maisonny (1952) and Borel-Maisonny (1951) suggest neurological defects which are apparently unrecognized as such. The majority of the case reports lead one to suspect that neurological abnormalities were unrecognized or not tested for. For example, no record of the "face-hand test" being performed is found in the available case records of familial dyslexia.

A "positive face-hand test" which is part of an "organic mental syndrome" (Bender, 1952) in adult patients is considered by Cohn (1951) to be "a fairly acceptable test of 'backwardness in children' past the age of 6 years." Fink and Bender (1953) believe that a normal face-hand response is an ability of "tactile discrimination acquired by the child during growth." Green and Fink (1954) state that a "positive face-hand test" showing errors of extinction only, and occurring with tactile stimulation alone, can be seen "occasionally in normal adults" whereas extinction occurring with both tactile and rubbing types of stimulation is "never found in normal adults or in patients with psychogenic disorders." It is this latter type of "positive face-hand test" that both father and youngest son exhibited bilaterally.

Abnormal responses to face-hand testing have been interpreted in a variety of ways and according to a number of hypotheses (Bender, 1952; Bender, Green and Fink, 1954; and Critchley, 1953). While not diagnostic of structural disease of the brain or of discrete localizing value, a positive face-hand test is indicative of a cerebral defect and suggests parietal lobe dysfunction.

The finding of right-left confusion or disordered "directional selection" is, however, reported in the literature on dyslexia (Borel-Maisonny, 1951; Launay and Borel-Maisonny, 1952; Galifret-Granjon, 1951). Launay (1952) not only reports that his dyslexia patients of 6 to 8 years of age all show "global" errors in this performance but also concludes "that there is objective evidence of difficulty in body scheme which shows itself in these subjects in discriminating their own two sides." He cites Galifret-Granjon's study which reported similar disordered directional selection in response to Head's tests. Bender and Schilder (1951) also note that "there is often a defect in right-left discrimination" in the specific reading disability cases. Eustis (1947) writes that "the essence of the disability is

confusion between the right and left directions or, more rarely, between up and down."

According to de Ajuriaguerra, Diatkine and Cahen (1951) rightness and leftness are acquired about the seventh or eighth year and Launay (1952) believes right-left confusion to be normal until after the mental age of 8. Thus both a positive face-hand and disordered directional selection can be interpreted as being either expressions of functional immaturity of the central nervous system or as the result of pathological lesions.

Right-left disorientation is a recognized acquired neurological abnormality, a cardinal feature of the Gerstmann syndrome (Gerstmann, 1940; Critchley, 1953) considered by Critchley to be a "true confusion in spatial orientation," and a suggestive sign of parietal lobe dysfunction.

Graphanæsthesia is not accorded the status of a clinical sign by Critchley (1953) although it is frequently considered a test of parietal lobe function and indicative of "cortical sensory" impairment. Despite Critchley's well-taken arguments against the use of graphanæsthesia as a "clinical sign" the finding is not normal and is here considered as an index of cerebral dysfunction suggestive of parietal lobe involvement.

The significance of the father's (A. W.) preference for the use of the left eye, right hand and right foot is less easily assessed. Orton (1925, 1937) was perhaps the first, and surely one of the most vehement, advocates of the thesis that the failure to develop unilateral eyedness, handedness and footedness reflected faulty cerebral dominance which is basic in reading disabilities. Orton (1943) reports a high incidence of mixed dominance in "strephosymbolic" children. His findings are similar to those of Monroe (1932), Eames (1935), and Dearborn (1931) and Skydsgaard (1942). On the other hand Johnston (1942), Hildreth (1945), Bennett (1938), Gates and Bond (1936), Smith (1950) and others have failed to statistically show that mixed dominance is greater in dyslexic than in control groups. Hallgren (1950) also fails to find any "relationship between eye and hand dominance and specific dyslexia." Johnston's (1942) is perhaps the most complex statistical analysis of the problem. Fink (1938), Selzer (1933), Walls (1951), Berner and Berner (1938, 1953) are among the ophthalmologists who have investigated eyedness and its relation to reading disabilities. Berner and Berner (1953) conclude that mixed hand-eye preference is truly significant in reading disabilities.

In addition to disagreement regarding the incidence of mixed hand-eye preference, there is severe criticism of testing methods and considerable doubt that handedness or eyedness are true indicators of cerebral dominance (Selzer, 1933; Crider, 1934, 1944; Wolfe, 1941; Twitmyer and Nathanson, 1933; Franz, 1933).

With this background of uncertainty and disagreement the mixed eye-

hand preference in one of the cases reported cannot be included as an abnormal finding without some reservations.

As might be expected the "aphasia testing" revealed the most interesting abnormalities.

Marshall and Ferguson (1939) have reported a case of "hereditary word-blindness" which is remarkably similar to the present case in so far as the Head Object tests are concerned. Their patient had "overcome a reading and speaking disability" but still had gross difficulty in writing the name of the objects shown to him and in writing from dictation. Marshall and Ferguson concluded that "the word-blind are limited chiefly by their inability to circumvent the visual speech associations by auditory and other channels."

Schilder (1944) came to a similar conclusion in stating that "the basic difficulty in congenital reading disability is the difficulty to differentiate the spoken word into its sounds and to put together the sounds of a word. Words and single sounds are brought into connexion with a written word and a written letter, but the written word and the written letter cannot be integrated and differentiated."

Analysis of the performance of B. W., the "reader" of the 3 cases reported here, reveals that the residual disturbance in these tests is that of writing from dictation. The father and youngest son have further difficulties. In addition to errors or failure to write from dictation, their performances are marred by minor errors in copying, difficulty in writing the name of the object shown to them, and trouble in matching the written name, read silently, with the object.

Head (1926) states that "written or printed material forms a further representation in visual terms of symbols of articulatory speech; in order that it may be understood certain conventional signs must be correctly apprehended and translated silently or aloud into verbal forms."

If Head's classification is followed these patients exhibit a nominal type of aphasia with a basic defect in the use of names as symbols. In fact the patient reported by Marshall and Ferguson (1939) can also be so classified and their emphasis upon a defect in "phonetic integration" is simply another way of stressing the relationship between visual and auditory verbal symbolization and does not alter the interpretation that their patient exhibited a partial nominal aphasia.

However, there is evidence that something more than a pure language disturbance exists in these patients. The tendency to confuse yellow and white and to rotate blocks in the Block Design test is difficult to ascribe to a language disturbance. The abnormal face-hand test and right-left disorientation are also not easily viewed as aphasic symptoms in the usual sense of that term implying disturbance in symbolic thinking and expression.

Disordered directional sense is considered by Critchley (1953) to be a

true disturbance in "spatial orientation" and not a verbal or semantic defect. The rotations detected in the Kohs block test are also best considered as errors in spatial orientation, perhaps a form of visual disorientation. Both are principally related to a parietal lobe function. Confusion of yellow and white is a defect primarily of the gnostic sphere and as detected in the two patients tested appears best considered as a form of visual agnosis rather than a language disturbance.

Thus, although these patients show evidence of aphasic language disturbance they also appear to suffer from agnostic difficulties as well, and no single basic defect is thus far discernible in the case material.

It is impossible to avoid comparison of the findings in these patients with hereditary dyslexia and other patients who have dyslexia as a result of acquired cerebral lesions. In this connexion it should be re-emphasized that "pure" alexia or dyslexia has yet to be convincingly demonstrated and as Critchley (1953) states, "Incomplete clinical examination will naturally endow the alexia with an appearance of isolation or specificity which may well be spurious. Most dyslexic patients prove to be afflicted by other parietal symptoms." Even the occipital visual verbal agnosia is "nearly always, if not always" accompanied by a homonymous hemianopsia and is a "pure word-blindness" only in the sense of being unaccompanied by agraphia (Nielsen, 1946; Symonds, 1953). Holmes' (1950) case of "word-blindness" had other abnormal signs referable to the parietal lobe.

As has been noted earlier, dyslexic or alexic symptoms are reported as occurring with lesions from frontal and occipital poles (Nielsen, 1946). However, one syndrome, the Gerstmann syndrome, is called to mind by some of the abnormalities found in this family. Interestingly enough a congenital case of Gerstmann's syndrome is cited by Critchley (1953).

The classical Gerstmann syndrome consisting of finger agnosia, right-left disorientation, acalculia and agraphia may be associated with "various other clinical symptoms, such as constructive apraxia, amnestic reduction of word finding, a certain, usually insignificant disturbance in the capacity to read, impairment of colour perception, absence of optokinetic nystagmus and disturbance of equilibrium." These manifestations "can undoubtedly be regarded as arising from involvement of border or neighbourhood tissue" (Gerstmann, 1940).

Critchley (1953) suggests that the dysgraphia of the Gerstmann's syndrome is probably a "writing dyspraxia" and not a disorder of speech. Others have been impressed with similarity of the dysgraphia of congenital dyslexia and that of Gerstmann's syndrome. In both "spontaneous writing and writing from dictation are as a rule considerably more disturbed than copying from a sample" (Hermann and Voldby, 1946). It appears to the present writer that a defect in language is more likely to be the explanation of the dysgraphia of congenital dyslexia. This is

perhaps also the case in Gerstmann's syndrome, or at least in the clinically observed modifications of the pure Gerstmann's syndrome. In both there appears to be a failure of integration of auditory and visual symbols of language rather than dyspraxic disturbance.

Attempts to explain the fundamental nature of Gerstmann's syndrome are reviewed by Critchley (1953) who does not come to any final conclusion except to imply that the configurational approach gives most promise. Gerstmann (1940) states that "it cannot be said thus far a conclusive solution of the problem has been provided." However, Stengel (1944) and Juba (1948) writing at a later date urged that the various components of the Gerstmann syndrome are the expression of a basic difficulty with Gestalt formation.

Duensing (1952) speaks of three stages of visual gnosis: (1) Gestalt seeing, (2) Gestalt recognition, and (3) object comprehension. He believes visual agnosia to be a defect in Gestalt recognition rather than perception. It is interesting to see how well Orton's (1925) concept of three cortical levels of integration of vision can be adapted to Gestaltic terminology. Orton believed that "word-blindness" was the result of a deficit at the third level of cortical visual function, the level of visual association or Duensing's third stage, object comprehension.

In addition to the visual disturbance, secondary to parietal lobe pathology, Critchley (1953) believes that the other findings in acquired parietal disease "fit most easily in the cadre of configurational psychology."

The clinical findings in the 3 cases reported here have features in common with some cases of acquired parietal lobe disease or injury. It therefore may be profitable to explore the Gestalt approach to the problem of hereditary dyslexia in the search for a fundamental inheritable defect.

Hirsch (1952), Pflugfelder (1948), Krise (1949, 1952), and Bender and Schilder (1951) are among those who view congenital dyslexia as the result of a fundamental disturbance in Gestalt function. Bender and Schilder state that "reading disability represents a clear-cut defect in the visual-motor field." Hirsch relates the dyslexia "to some more basic difficulty in differentiating foreground from background," and Pflugfelder traces the reading disability to "weakness in visual organization." Krise sees the frequently reported reversal tendencies as a result of distorted figure-ground relationships.

The abnormalities noted in the case material presented above may all be viewed as the result of disturbed figure-ground relationships. Thus right-left confusion and abnormal face-hand testing can be considered as an expression of "the inability of the individual to compare and contrast sensory relationships" (Reinhold, 1954) and thus correctly relate spatially parts of both extrapersonal and personal space into an organized whole.

The abnormal responses in the Block Design test are similar to those

reported by McFie, Piercy and Zangwill (1950) and regarded by them as the result of disturbed perception of spatial relationships.

The discrepancy between the ability to copy and the ability to write spontaneously or from dictation, was described as a disturbance in "phonetic integration" by Marshall and Ferguson (1939). Bender and Schilder (1951) view this as "a special incapacity to relate visual structure of a word to its auditory structure. This is probably due to the difficulty in experiencing the total auditory and visual Gestalt of the word as a sign."

The assumption that the fundamental defect in hereditary dyslexia is a disturbance in Gestalten formation not only permits the explanation of the numerous variations and inconsistencies which appear in the literature, but also suggests a theoretical basis for the monohybrid dominant form of inheritance in hereditary dyslexia. If viewed as the results of a defect in the formation of Gestalten, the findings in the 3 cases presented here are more readily comprehended in a familial genetic setting. Unless such a basic defect is postulated there appears to be no other way to interrelate the 3 cases clinically.

During the past four years a number of non-familial cases of congenital dyslexia have been examined by the writer (Rabinovitch, Drew *et al.*, 1955). Without exception, these patients show one or more of the defects detected in the cases presented above. Thus in addition to the reading disability, a defect in directional selection, mixed hand-eye preference, face-hand test abnormalities, reversals, auditory visual phonetic disintegration, spatial disorientation are found in varying combinations. No constant neurological sign is present but if these various findings are interpreted as Gestalten disturbances then the entire symptom complex becomes a coherent entity.

It is believed that the dyslexia observed in the family presented here is due to a basic defect in Gestalt recognition which interferes with visual-verbal comprehension. Not only reading, but writing, spatial orientation and auditory-visual integration may be affected by this defect which is perhaps the result of a failure of, or delay in, maturation of the functions of the parietal lobes. Although certain reflex abnormalities in 2 of the cases here presented implicate the left hemisphere, there is insufficient evidence to draw any conclusions regarding the relative involvement of dominant or other hemisphere. It is possible that failure to develop complete dominance (Orton, 1937) may be the patho-physiologic mechanism by which Gestalt function is disrupted. However, since mixed "sidedness" is not a constant correlate of congenital dyslexia it appears more likely that mixed dominance is but one result of a more basic disturbance rather than the primary ætiological factor.

If viewed as defects in Gestalt function many of the reported correlates of reading disability become comprehensible as parts of a single fundamental defect. Reversals, mirror-writing, mixed hand-eye preference,

spatial disorientation, phonetic disintegration and other abnormalities often considered basic in congenital dyslexia are best viewed as variant manifestations of the fundamental defect in correct figure-ground recognition in both familial and non-familial congenital dyslexia. Attempts to comprehend and statistically analyse case material in terms of any single observed abnormality have not been successful. It is believed that the inconsistencies, confusion and apparently diametrically opposed findings reported in the literature and observed clinically can best be resolved by interpreting the findings in a configurational setting.

Summary and Conclusion

A review of the literature concerning hereditary dyslexia reveals little information relative to the neurological correlates of the condition but does present good evidence that a dominant mode of inheritance is responsible for the familial form of "word-blindness." It is argued that if this be the case either "pure" word-blindness exists in a genetically transmissible form or else some other unitary defect must be postulated to explain the familial occurrence of the symptom.

The examination of 3 cases of familial dyslexia reveals certain neurological findings which are believed to be comparable to abnormalities often seen in association with acquired "word-blindness" due to involvement of the parietal lobes. The frequently reported absence of neurological findings in congenital word-blindness is not borne out by the present investigation.

It is suggested that apparent inconsistencies between the individual cases reported here can be resolved by viewing the common defect as a disturbance in Gestalt function which is inherited as a dominant trait. There is some reason to believe that delayed development of the parietal lobes is the anatomical substrate of this disturbance in Gestalt recognition.

BIBLIOGRAPHY

Anderson, M., and Kelly, M. (1931) Smith College Studies in Social Work, **2**, 46.
Bachmann, F. (1927) *Abh. Neurol. Psychiat. Psychol.* (Heft) **40**.
Bakwin, R. M., and Bakwin, H. (1948) *J. Pediat.*, **32**, 465.
Bender, L., and Schilder, P. (1951) *J. Clin. exp. Psychopath.*, **12**, 147.
Bender, M. B. (1952) "Disorders in Perception." Springfield, Illinois.
——, Green, M. A., and Fink, M. (1954) *Arch. Neurol. Psychiat., Chicago*, **72**, 233
Bennett, C. C. (1938) An inquiry into the genesis of poor reading. Teachers College, Columbia University, Contributions to Education No. 755.
Berkhan, O. (1917) *Neurol. Zbl.*, **36**, 914.
Berner, G. E., and Berner, D. E. (1938) *Arch. Ophthal., N.Y.*, **20**, 829.
——, —— (1953) *Arch. Ophthal., N.Y.*, **52**, 603.
Blanchard, P. (1946) *Psychoanal. Study Child.*, **2**, 163.
Blau, A. (1946) "The Master Hand." New York.
Borel-Maisonny, S. (1951) *Folia phoniatr., Basel*, **3**, 86.
Burt, C. (1935) "The Subnormal Mind." Oxford.

CHANCE, B. (1913) *N.Y. med. J.*, **97**, 697.
CLAIBORNE, J. H. (1906) *J. Amer. med. Ass.*, **47**, 1813.
CLAPARÈDE, (1917) *Neurol., Zbl.*, **36**, 572.
COHN, R. (1951) *Neurology*, **1**, 119.
CRIDER, B. (1934) *Childhood Educ.*, **10**, 238.
—— (1944) *J. Gen. Psychol.*, **31**, 179.
CRITCHLEY, M. (1953) "The Parietal Lobes." London.
DE AJURIAGUERRA, J. (1951) *Enfance*, **4**, 389.
——, DIATKINE, and CAHEN (1951) *Sauvegarde*, p. 608 (cited by LAUNAY, 1952*b*).
DEARBORN, W. F. (1931) *Psychol. Bull.*, **28**, 704.
DREWS, E. M. (1954) Thesis, University of Michigan (unpublished).
DUENSING, F. (1952) *Arch. Psychiat. Nervenkr.*, **188**, 131.
EAMES, T. H. (1935) *J. educ. Res.*, **29**, 1.
ELLIS, A. (1949) *J. Cons. Psychol.*, **13**, 56.
EUSTIS, R. S. (1947*a*) *New Engl. J. Med.*, **237**, 243.
—— (1947*b*) *J. Pediat.*, **31**, 448.
FILDES, L. G. (1921) *Brain*, **44**, 286.
FINK, M., and BENDER, M. B. (1953) *Neurology*, **3**, 27.
FINK, W. H. (1938) *Arch. Ophthal.*, **19**, 555.
FISHER, J. H. (1905) *Ophthal. Rev.*, **24**, 315.
FRANZ, S. I. (1933) *J. exp. Psychol.*, **16**, 873.
GALIFRET-GRANJON (1951) *Enfance*, **4**, 445.
GANN, E. (1945) "Reading Difficulty and Personality Organization." New York.
GATES, A. I. (1927) "The Improvement of Reading." New York.
—— (1941) *J. genet. Psychol.*, **59**, 77.
——, and BOND, G. L. (1936) *J. Educ. Psychol.*, **27**, 450.
GERSTMANN, J. (1940) *Arch. Neurol. Psychiat., Chicago*, **44**, 398.
GREEN, M. A., and FINK, M. (1954) *Neurology*, **4**, 211.
HALLGREN, B. (1950) *Acta psychiat. Kbh., Suppl.*, 65.
HEAD, H. (1926) "Aphasia and Kindred Disorders of Speech." Cambridge.
HERMANN, K., and VOLDBY, H. (1946) *Acta psychiat., Kbh.*, **21**, 349.
HILDRETH, G. (1945) *J. appl. Psychol.*, **29**, 82.
HINSHELWOOD, J. (1917) "Congenital Word-blindness." London.
HIRSCH, K. (1952) *Folia phoniat., Basel*, **4**, 231.
HOLMES, G. (1950) *Folia psychiat. neerl.*, **53**, 279.
IRVINE, R., *et al.* (1941) *Amer. J. Ophthal.*, **24**, 779.
JACKSON, J. (1944) *J. genet. Psychol.*, **65**, 113.
JOHNSTON, P. W. (1942) *Monogr. Soc. Res. Child Developm.*, Vol. 7, No. 2.
JONES, M. M. W. (1944) *School & Soc.*, **60**, 238.
JUBA, A. (1948) *Schweiz. Arch. Neurol. Psychiat.*, **61**, 217.
KERR, J. (1897) *J. Statistic. Soc.*, **60**, 613.
KRISE, E. M. (1949) *Elem. Sch. J.*, **49**, 278.
—— (1952) *J. Educ. Psychol.*, **43**, 408.
LARSEN, C. A. (1947) *Psychol. Studien*, 2nd Serie, No. 6.
LAUBENTHAL, F. (1936) *Z. ges. Neurol. Psychiat.*, **156**, 329.
—— (1938) *Z. ges. Neurol. Psychiat.*, **163**, 233.
—— (1941) *Der Erbarzt.*, **9**, 156.
LAUNAY, C. (1952*a*) *Sem. Hôp. Paris*, **28**, 1459.
—— (1952*b*) *Sem. Hôp. Paris*, **28**, 1463.
——, and BOREL-MAISONNY, S. (1952) *Sem. Hôp. Paris*, **28**, 1455.
MCCREADY, E. B. (1926) *Amer. J. Psychiat.*, **6**, 267.
MCFIE, J., PIERCY, M. F., and ZANGWILL, O. L. (1950) *Brain*, **73**, 167.
MARSHALL, W., and FERGUSON, J. H. (1939) *J. nerv. ment. Dis.*, **89**, 164.

MEYER, H., NORGAARD, B., and TORPE, H. (1943) Meddlelser fra Dansklaererforen.
MONROE, M. (1932) "Children Who Cannot Read." Chicago.
MORGAN, W. P. (1896) *Brit. med. J.*, **2**, 1378.
NIELSEN, J. M. (1946) "Agnosia Apraxia, Aphasia." 2nd edition, New York.
ORTON, S. T. (1925) *Arch. Neurol. Psychiat., Chicago*, **14**, 581.
—— (1928) *J. Amer. med. Ass.*, **90**, 1095.
—— (1937) "Reading, Writing and Speech Problems in Children." New York.
—— (1943) *Arch. Ophthal., N.Y.*, **30**, 707.
PEARSON, G. H. J. (1952) *Psychoanal. Study Child.*, **7**, 322.
PFLUGFELDER, G. (1948) *Mschr. Psychiat. Neurol.*, **115**, 55.
PRESTON, M. I. (1940) *Amer. J. Orthopsychiat.*, **10**, 239.
RABINOVITCH, R. D., DREW, A. L., DE JONG, R.N., INGRAM, W., and WITHEY, L. (1955) *Proc. Ass. Res. nerv. Dis.*, **34** (in press).
REINHOLD, M. (1954) *Neurology*, **4**, 128.
RIESE, W. (1954) *Bull. Hist. Med.*, **28**, 237.
RØNNE, H. (1936) *Trans. Ophthal. Soc. U.K.*, **56**, 311.
RUTHERFURD, W. J. (1909) *Brit. J. Child. Dis.*, **6**, 484.
SCHILDER, P. (1944) *J. genet. Psychol.*, **65**, 67.
SELZER, C. A. (1933) Harvard Monographs in Education, No. 12, Cambridge, Mass.
SKYDSGAARD, H. B. (1942) "Den konstitutionelle dyslexi." Kobenhavn.
SMITH, L. C. (1950) *J. exp. Educ.*, **18**, 321.
STENGEL, E. (1944) *J. ment. Sci.*, **90**, 753.
STEPHENSON, S. (1907) *Ophthalmoscope*, **5**, 482.
STEWART, R. S. (1950) *Amer. J. Orthopsychiat.*, **20**, 410.
SYMONDS, C. (1953) *J. Neurol. Neurosurg. Psychiat.*, **16**, 1.
THOMAS, C. J. (1905) *Ophthalmoscope*, **3**, 380.
TWITMYER, E. B., and NATHANSON, Y. (1933) *Psychol. Clin.*, **22**, 141.
VARIOT, G., and LECOMTE (1906) *Gaz. Hôp., Paris*, **79**, 479.
WALLS, G. L. (1951) *Arch. Ophthal., N.Y.*, **45**, 387.
WITMER, L. (1907) *Psychol. Clin.*, **1**, 53.
WITTY, P., and KOPEL, D. (1936*a*) *J. educ. Res.*, **29**, 449.
——, —— (1936*b*) *J. educ. Psychol.*, **27**, 19.
——, —— (1939) "Reading and the Educative Process." Boston.
WOLFE, L. S. (1941) *Pedag. Sem. and J. genet. Psychol.*, **58**, 45.
WOLFF, G. (1916) *Korresp. Bl. schweiz. Arx.*, **46**, 237.
YACORZYNSKI, G. K. (1949) *J. genet. Psychol.*, **41**, 111.

SPINAL EFFERENT PATHWAYS FROM THE SUPPLEMENTARY MOTOR AREA

BY

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THE supplementary motor area discovered by Penfield and Welch (1949, 1951) and by Woolsey (Woolsey and Settlage, 1950; Woolsey *et al.*, 1950, 1952) on the medial aspect of the first frontal convolution in man and monkeys, has now gained recognition as a distinct motor field. In monkeys, it occupies about the posterior half of Brodmann's area 6 on the mesial surface of each cerebral hemisphere and on the superior bank of the cingulate sulcus. It comprises, in addition, the portion of area 4 also in the cingulate sulcus as well as a narrow segment of this area adjacent to area 6, on the mesial surface. Stimulation of the supplementary motor area in monkeys produces movements of the contralateral somatic musculature which are of a different type from the ones obtained by excitation of the precentral cortex: they are slower, more tonic, more "postural." These movements can be produced even after excision of the precentral motor cortex in monkeys and, in man, they have been obtained after ablation of the pre and postcentral cortex (Penfield and Jasper, 1954).

Excision of one supplementary motor area, as recently demonstrated by Travis (1955*b*), produces in the contralateral extremities a transient hypertonicity and a grasp reflex. These signs are accentuated, prolonged and are accompanied by contractures of the limbs, and postural changes if the opposite supplementary motor area is also removed. Little paralysis is seen after these lesions, which is in striking contrast with the results of damage to the precentral motor cortex (Travis, 1955*a*). The supplementary motor area being thus a physiologically well-differentiated motor field, the question of its efferent pathways naturally came to mind. In spite of numerous studies of cortical efferent pathways, with particular reference to the origin of the pyramidal tract, there is little information available in the literature concerning the efferent pathways from the supplementary motor area. We have therefore undertaken to trace these pathways to the spinal cord by means of an electrophysiological method.

Materials and Methods

Our studies were carried out on 7 macaque monkeys (*Macaca mulatta*) and 1 African green monkey (*Cercopithecus æthiops sabæus*), all young adults weighing 4 to 5 kg.

Light and prolonged anæsthesia was produced by frequent intravenous injections of small quantities of pentobarbital sodium.

The animals were postured prone with the neck maintained in moderate flexion by a specially constructed head-holder. In this fashion, after a craniectomy and a laminectomy had been carried out, the cerebral cortex, the posterior fossa and the upper cervical cord were readily accessible simultaneously.

The supplementary motor area and other parts of the motor cortex were stimulated with short duration electrical pulses (square wave, 0·25 msec. duration) by means of monopolar "silver ball" electrodes with a surface of contact measuring less than 1 mm.² (diffuse electrode to scalp).

Recording was done at various levels in the spinal cord and medulla oblongata with fine needle electrodes (0·06–0·1 mm.), used either singly against a diffuse reference or in pairs, 0·5 mm. apart. Throughout each level, a systematic search for evoked responses was carried out, millimetre by millimetre. The signal obtained was fed to a four-stage condenser coupled amplifier and the responses were photographically recorded with a Cossor No. 1049 cathode-ray oscillograph whose sweep was triggered by the stimulator.

Results

A. The response.—The response obtained in the cord when the motor cortex was stimulated with a submaximal single shock varied to a great extent in form, amplitude and latency, depending upon the level at which the recording was made, the region explored within the cord at a given level and the area of cortex stimulated (figs. 1, 2, 3, 4, and 8).

We have found the response to be always composed of positive potentials (downward displacement of the trace), followed by a slight but prolonged negativity, when recorded intraspinally with a monopolar electrode against a diffuse reference (figs. 5, 6, and 7). In some of our experiments, however, because of the use of bipolar electrodes, such responses appeared sometimes as upwards, sometimes as downwards or mixed deflections (figs. 1, 2, 3, 4, and 8).

Regardless of this, we always found each response to consist of two distinct groups of potentials: (1) an early stable component, invariable in form, amplitude and latency for given parameters in successive stimulations; (2) a group of irregular waves of longer latency, following the first at variable intervals and very labile in appearance. The first is called the direct response or "D" wave, and the second the indirect response or "I" wave, as suggested by Patton and Amassian (1952, 1954*a* and *b*) and Wall, Rémond and Dobson (1952).

B. Rate of conduction.—The speed at which these impulses were conducted was found by Patton and Amassian (1954*a* and *b*) to be between 55 and 68 meters/sec. in the upper region of the pyramidal tract in monkeys and somewhat slower at lower levels. In our experiments, the velocity of impulses originating in the supplementary motor area was higher. Fig. 1

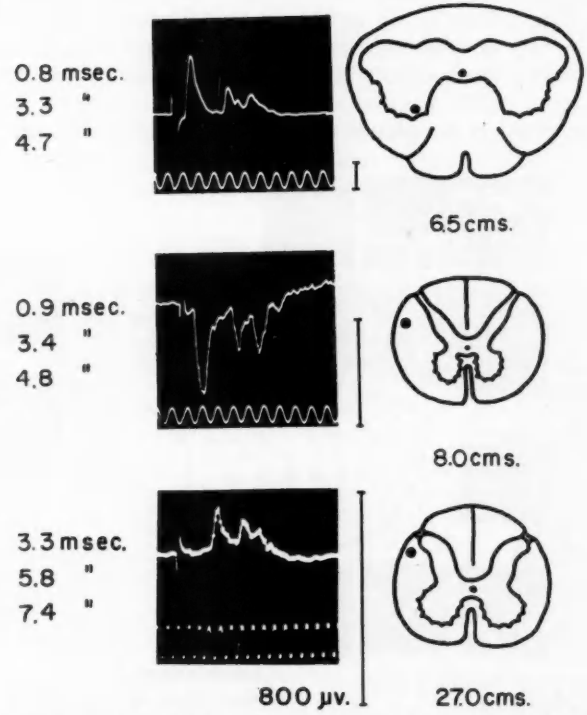

FIG. 1.—Responses to stimulation of supplementary motor area (single shock, 0·25 msec. duration, 8·5 volts). Bipolar recording in the crossed pyramidal tract, (*a*) just below the pyramidal decussation, (*b*) at the level of the arch of C2, (*c*) at the level of the arch of T12. Time scale, 1,000/sec. The "latencies" of the three most prominent components of the response are indicated on the left of the figure. The distance in cm. between stimulation and recording points is given on the right, for each level.

illustrates an experiment in which a conduction velocity of 89 meters/sec. was found from the cortex to the level of the posterior arch of C2 (8·0 cm., 0·9 msec.) and of 79 meters/sec. from the arch of C2 to the arch of T12 (19 cm., 2·4 msecs.).

According to Hursch's (1939) formula (the diameter of a fibre in micra is equal to 6·0 times its conduction velocity in meters/sec.), a fibre conduct-

ing at 89 meters/sec. should have a diameter of 89/6·0 = 14·8 micra. This falls well within the limits of fibre sizes (1–20 micra) reported by Häggqvist (1937) for the pyramidal tract of the monkey and implies that the response must be conducted over the larger fibres in the pyramidal tract.

C. Distribution of responses in the cord.—Systematic exploration of the cord at C2, millimetre by millimetre, anteroposteriorly and laterally revealed a very definite topographical arrangement of the responses to stimulation of a single cortical point in either the precentral or the supplementary motor areas.

Fig. 2 represents samples of these responses when the *left precentral*

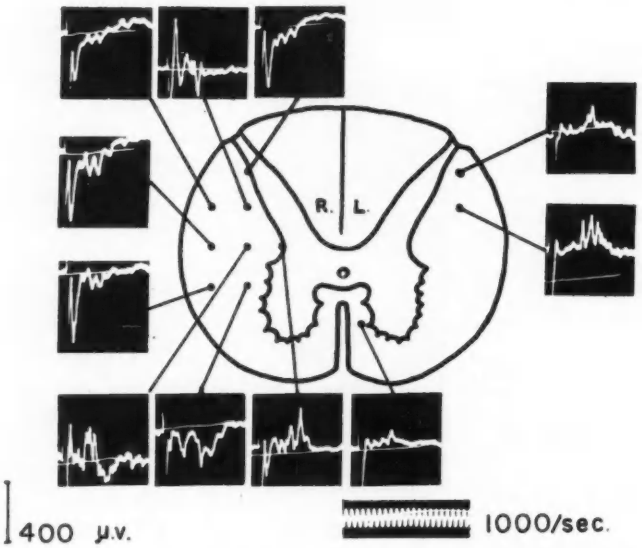

FIG. 2.—Responses to stimulation of the *left precentral motor area* (0·25 msec. 8·5 volts). Bipolar recording in a plane across the spinal cord at C2. The responses are clearly grouped in the region of the *right* (*contralateral*) pyramidal tract. A few responses of low amplitude are also picked up in the ipsilateral ventral and lateral columns (note relatively small "D" waves).

arm area was stimulated. As could be expected from anatomical and physiological evidence already at hand, most of the evoked potentials were picked up in the dorsal part of the right (contralateral) lateral column, in the region occupied by the lateral pyramidal tract (crossed pyramidal tract). Actually, responses of high amplitude were recorded on that side over an area larger anteriorly and mesially than the pyramidal tract could be expected to cover. This, we felt, could be explained, at least in part

by fibres leaving the tract and running into the grey matter, at the base of the posterior horn where Hoff and Hoff (1934, 1935) have shown them to synapse.

Potentials of lesser amplitude and of different form were also obtained from the *left* (ipsilateral) lateral column at two recording stations and in the ventral column, close to the mid-line, on the *left*, in the region of the direct (uncrossed) pyramidal tract (fig. 2).

No evoked potentials were recorded from the rest of the cord. Some low voltage activity was always obtained from the grey matter but it was unrelated to cortical stimuli and some of it was obviously due to injury.

When the stimulating electrode was shifted on the *left* hemisphere from the precentral to the supplementary motor area, the pattern of representation in the cord was modified in a striking manner by the appearance of an important contingent of responses in the lateral column *of the same side*, over its posterior 2/3 (fig. 3). The responses obtained in

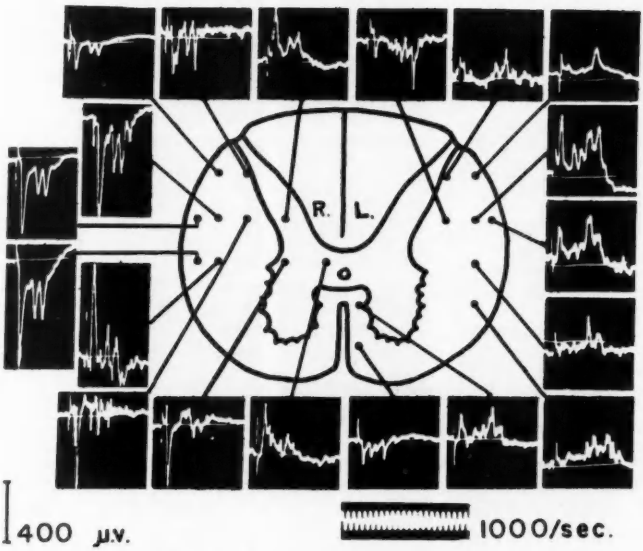

FIG. 3.—Responses to stimulation of the *left supplementary motor area* (0·25 msec., 8·5 volts). Bipolar recording as in fig. 2. Note how important the ipsilateral responses are, in comparison to what they were in the preceding figure.

the lateral column on the opposite side and in the ipsilateral anterior column were indistinguishable, except for minor details, from those evoked from the precentral motor cortex and there was no evidence that they were carried by separate pathways in the cord.

It may be said in passing that we could find in the cord no somatotopic

arrangement or stratification of fibres from various portions of the precentral motor cortex, as exists for centripetal sensory fibres. The same applied to the bulbar pyramids, as Landau (1952) has shown.

These findings were easily verified in a number of animals and it became apparent that the supplementary motor area had a much more important representation on the ipsilateral side of the cord than did the precentral motor area.

D. Variations in response.—Potentials were not identical in all tracts of the cord; fig. 4 illustrates their various appearances in an experiment

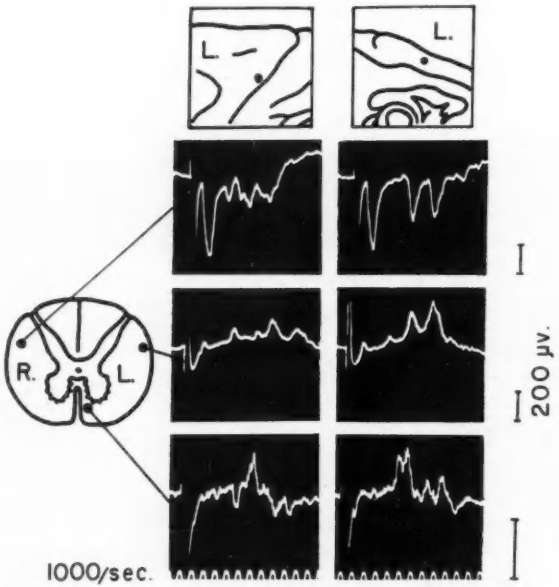

FIG. 4.—Samples of responses to stimulation of the *left precentral* motor area and of the left supplementary motor area, recorded at C2 in the contralateral lateral column (top line), in the ipsilateral lateral column (middle line), in the ipsilateral ventral column (bottom line). (Bipolar recording.)

where the precentral and the supplementary motor areas were stimulated successively for each recording point.

In the contralateral pyramidal tract, the response consisted of a very prominent "D" (direct) wave followed by 3 to 5 "I" (indirect) waves of low to moderate amplitude; the latter appeared to be less numerous but of higher voltage, when the supplementary area was stimulated and then were often separated from the initial "D" wave by a "silent" interval of 2–3 msecs. (*see also* figs. 2 and 3).

In the ipsilateral lateral column, potentials produced by excitation of the precentral motor cortex were particularly noticeable by the almost complete absence of a "D" wave. The response consisted mainly in groups of "I" waves, extremely variable in size and number (figs. 2 and 4). On the other hand, stimulation of the supplementary area always yielded evoked potentials of higher voltage, most of the time with good "direct" components (figs. 3 and 4).

In the ipsilateral ventral tract, the same observations were made as have been related in the preceding paragraph, with the difference that the responses were of much lower amplitude. They were not studied in detail (figs. 2, 3, and 4).

E. Nature of response.—Patton and Amassian (1952, 1954*a* and *b*) and Zanchetti (1954) have come to the conclusion that "D" waves result from direct excitation of large pyramidal units while "I" waves are due

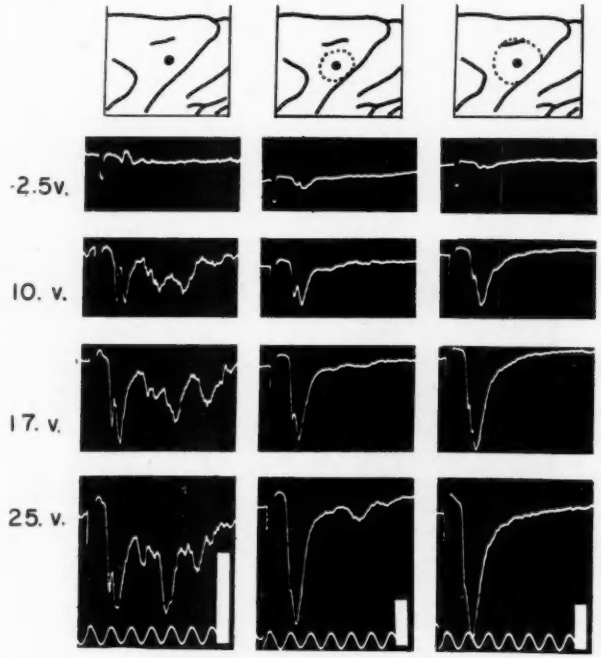

FIG. 5.—Effect on the response recorded in the crossed pyramidal tract after cortical excision at the point stimulated (0·25 msec. shock, voltages as indicated). First column: cortex intact. Second column: cortex excised over an area 0·8 cm. in diameter. Third column: Area of cortical ablation 1·2 cm. in diameter. (Monopolar recording, all deflections are positive. Amplifier gains have had to be lowered after excision.)

to firing via cortical interneurones. Our own experiments lend support to this view. Fig 1 shows that "D" and "I" waves travel down the cord at the same speed, since duration of the entire response is not significantly longer at T12 than it is in the medulla oblongata. As it seems unlikely that they take origin within the medulla or the cord itself, the "I" waves must therefore consist of potentials which are delayed either at a point between the cortex and the medulla or at the cortex itself. The last alternative seems confirmed by cortical excision and stimulation of the underlying white matter; "I" waves become progressively more difficult to elicit as the area of grey matter removed around the point stimulated is made larger; whereas, the "D" complex is enhanced by direct excitation of the white matter (fig. 5; gains had to be reduced after cortical ablation).

Local application of strychnine sulphate 1/1,000 to the cortex stimulated, on the other hand, increases the number and the amplitude of the "indirect" waves, without affecting the "D" potentials (fig. 6) bringing still further confirmation of the cortical origin of "I" waves.

Like Patton and Amassian, we have also found the greater sensitivity of the "indirect" waves to anæsthetic agents. This is demonstrated in

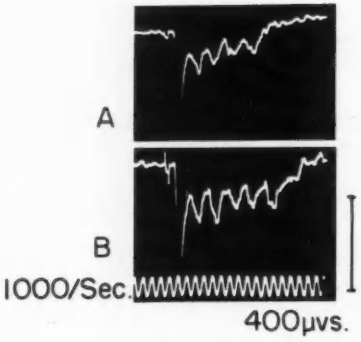

FIG. 6.

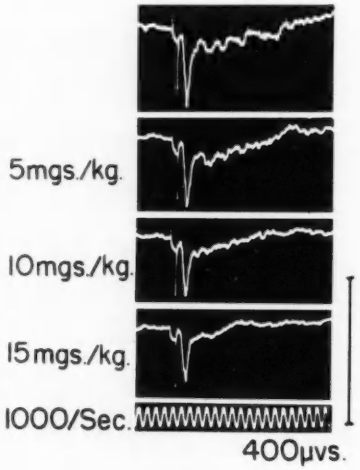

FIG. 7.

FIG. 6.—Effect of local application of strychnine sulphate 1/1,000 to the cortex stimulated. 0·25 msec., 10 volts, single shocks applied to the precentral motor area. Monopolar recording in the contralateral pyramidal tract at C2: A, Before the application of strychnine. B, Three minutes after its application.

FIG. 7.—Effect of general anæsthesia on the response to precentral motor area stimulation. Recording station and parameters of stimulation, same as in fig. 6. The first line shows the response in the animal awake; the others illustrate the effects of increasing dosages of pentobarbital sodium administered intravenously.

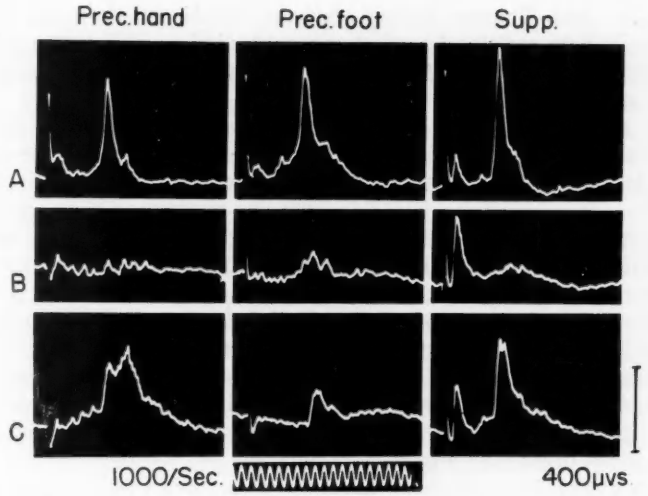

FIG. 8.—Responses picked up in the ipsilateral (direct) lateral pyramidal tract at C2 (bipolar recording), following stimulation of the precentral hand area, precentral foot area and supplementary motor area. Line A illustrates the responses from intact cortex; the supplementary area gives the highest "D" and "I" waves in that tract. Line B shows the striking depression of the "I" complex after a 7 mm. deep subpial incision has been made in the cortex above and behind the supplementary area to isolate it from the rest of the motor cortex. The large "D" response from the supplementary area remains (it now appears larger, probably because of a slight shift of the recording electrode). Line C shows the reappearance of the "I" waves, 10 minutes after the section.

fig. 7 in which the "I" component is seen to disappear from the response as the concentration of pentobarbital sodium is increased. It may be noted that local trauma to the cortex also causes a depression of the indirect potentials for a short period of time after which, if the cortex stimulated has not been itself damaged, they gradually reappear. Fig 8 illustrating an experiment in which a subpial section has been carried out between the precentral and the supplementary areas shows this phenomenon very well.

DISCUSSION

The origin of the pyramidal tract has always been a debated question among anatomists and neurophysiologists, particularly as regards the contribution of the "premotor" cortex to this tract and the origin of the ventral and of the lateral uncrossed tracts.

Schäfer (1883) and Sherrington (1894) were among the first to demonstrate in monkeys the existence of degenerated uncrossed fibres in the lateral column on the same side as a lesion in the "cord area" of one hemisphere.

Dejerine and Thomas (1896) reported similar findings in human hemiplegics with unilateral cortical or capsular lesions. They also pointed out that a third group of fibres, which also did not cross, remained in the anterior column on the same side.

Hoff and Hoff (1934, 1935) always found degenerated "boutons terminaux" on both sides of the cord, after unilateral motor or "premotor" cortex lesions but always more numerous on the side opposite to the lesion.

Kennard (1935) thought that the "premotor" area sent down a greater proportion of its fibres ipsilaterally than the "motor" area but that only the latter contributed to the formation of the ventral direct tract. Mettler (1935, 1944) and Levin (1936) disagreed and saw little or no degeneration in the pyramidal tracts following lesions of area 6 (Brodmann's).

Verhaart and Kennard (1940), in thermocoagulation experiments on areas 4, 4s and 6, failed to reproduce Kennard's earlier findings and were unable to demonstrate any important contingent of cortico-spinal fibres from regions other than area 4.

Lassek (1941, 1942, 1943, 1948), however, showed in his cell and fibre counts of the motor cortex and pyramids, that the latter could not take origin only in the pyramidal cells of area 4 but must also stem from regions anterior to it.

Following electrical stimulation of the bulbar pyramids in monkeys, Woolsey and Chang (1948) recorded antidromic potentials over areas 9, 6, 4, 3, 1, 2, 5, and 7 of Brodmann; they did not, however, explore the mesial surface of area 6.

In our experiments, the presence of "direct" waves in the pyramidal tracts, on both sides of the cord, after electrical stimulation of one supplementary motor area, is evidence that this region projects directly into the pyramidal tracts, in a manner similar to the precentral motor cortex, that it gives rise to direct as well as crossed pyramidal fibres and that it must therefore be considered as part of the "pyramidal cortex."

As in the case of the precentral cortex, the crossed group of fibres is the most important but the supplementary motor area contributes a larger proportion of direct fibres to the ipsilateral cortico-spinal tract, as judged by the higher amplitude of the "D" waves and the wider distribution of the responses in the lateral column. Such a bilateral projection may explain the movements obtained by Penfield, in the extremities of both sides, after electrical stimulation of that area, in unanæsthetized patients (Penfield, 1950; Penfield and Jasper, 1954; Penfield and Rasmussen, 1950; Penfield and Welch, 1949, 1951).

It also provides support to Travis' (1955*b*) observation that "unilateral lesions caused only minor deficits, whereas, simultaneous bilateral removals yielded more prominent effects on posture and tones" from which she concluded that the supplementary motor area was a "bilateral system."

Differences in form between the supplementary and the precentral indirect responses, undoubtedly represent differences in the pattern of interneuronal connexions at the cortical level. By their "modulating" effect on the spinal internuncial system, they may be responsible for the special character of the movements produced by excitation of each of these areas.

No attempt has been made to record responses above the medulla oblongata in this series of experiments but it has been explored on one occasion, just above the decussation of the pyramids. The most important group of responses, by far, was found in the pyramid on the side of stimulation, as one would have expected. A few weak potentials were picked up, however, in the postero-lateral portion of the medulla on the opposite side and were thought to originate in fibres which had crossed early, since the bulk of the crossed pyramidal fibres were found one or two millimetres lower, in the same area.

Above the decussation, within the contralateral pyramid, a response was obtained only in one recording point. It appeared in the form of very low amplitude "I" waves following precentral stimulation. Excitation of the supplementary motor area never gave evoked potentials in that portion of the medulla.

We do not imply from this that the supplementary motor area's only efferent pathways lie within the pyramidal tracts; there are no doubt larger numbers of association and extrapyramidal fibres leaving the area. Still incomplete Marchi studies following small lesions limited to one supplementary area have already shown clearly groups of such fibres fanning out towards the adjacent motor cortex and towards the cortex of the opposite hemisphere via the corpus callosum. Others, going down in the anterior limb of the internal capsule will probably be found to make connexions with nuclei of the base.

Summary and Conclusions

In monkeys, the supplementary and precentral motor areas were stimulated electrically, and evoked potentials were recorded in the spinal cord and medulla oblongata.

The recorded response to a single short duration shock consists in an initial stable, short latency, "direct" component, followed by a more complex, irregular "indirect" wave.

Both these components are electrically positive at the electrode tip, against a diffuse reference.

General anæsthesia, trauma to the cortex in the vicinity of the stimulating electrode and ablation of the grey matter at the point stimulated all reduce or abolish the "I" waves in the response; whereas, local application of strychnine enhances them, confirming Patton and Amassian's conclusions that the "I" waves are due to firing of cortical interneurones.

Stimulation of the white matter after cortical ablation, on the other hand, increases the amplitude of the "D" waves, indicating that they are the result of direct stimulation of pyramidal neurones.

The conduction velocity for responses originating in the supplementary motor area has been found to be of the order of 89 meters/sec. from the cortex to the level of C2 and of 79 meters/sec. from C2 to T12.

The supplementary motor area projects directly into the pyramidal tract in a manner similar to the precentral motor area and independently from it; it must therefore be considered as part of the "pyramidal motor cortex."

The supplementary motor area has also a much more important ipsilateral projection in the lateral column of the spinal cord than the precentral motor area; it can thus be looked upon as a truly "bilateral system."

Both areas contribute fibres to the ipsilateral ventral column (direct ventral pyramidal tract).

In the crossed pyramidal tract, only minor variations differentiate the responses from both cortical areas; in the direct lateral tract, the differences are greater, the most important one being the almost complete absence of "D" wave in the response originating in the precentral motor cortex.

REFERENCES

DEJERINE, J., and THOMAS, A. (1896) *Arch. Physiol. norm. path.*, **8**, 277.

HÄGGQVIST, C. (1937) *Acta psychiat., Kbh.*, **12**, 457.

HOFF, E. C. (1935) *Arch. Neurol. Psychiat., Chicago*, **33**, 687.

——, and HOFF, H. E. (1934) *Brain*, **57**, 454.

HURSCH, J. B. (1939) *Amer. J. Physiol.*, **127**, 131.

KENNARD, M. A. (1935) *Arch. Neurol. Psychiat., Chicago*, **33**, 698.

LANDAU, W. M. (1952) *Electroenceph. clin. Neurophysiol.*, **4**, 527.

LASSEK, A. M. (1941) *J. comp. Neurol.*, **74**, 193.

—— (1942) *J. nerv. ment. Dis.*, **95**, 721.

—— (1943) *J. comp. Neurol.*, **79**, 407.

—— (1948) *Res. Publ. Ass. nerv. ment. Dis.*, **27**, 106.

LEVIN, P. M. (1936) *J. comp. Neurol.*, **63**, 369.

METTLER, F. A. (1935) *J. comp. Neurol.*, **61**, 509.

—— (1944) *Proc. Soc. exp. Biol., N.Y.*, **57**, 111.

PATTON, H. D., and AMASSIAN, V. E. (1952) *Fed. Proc.*, **11**, 119.

——, —— (1954*a*) *Fed. Proc.*, **13**, 108.

——, —— (1954*b*) *J. Neurophysiol.*, **17**, 345.

PENFIELD, W. (1950) *Arch. Psychiat. Nervenkr.*, **185**, 670.

——, and JASPER, H. H. (1954) "Epilepsy and the Functional Anatomy of the Human Brain." Boston.

——, and RASMUSSEN, T. (1950) "The Cerebral Cortex of Man." New York.

PENFIELD, W., and WELCH, K. (1949) *Trans. Amer. neurol. Ass.*, **74,** 179.

——, —— (1951) *Arch. Neurol. Psychiat., Chicago*, **66,** 289.

SCHÄFER, E. A. (1883) *J. Physiol.*, **4,** 316.

SHERRINGTON, C. S. (1894) *Lancet*, **1,** 265.

TRAVIS, A. M. (1955*a*) *Brain*, **78,** 155.

—— (1955*b*) *Brain*, **78,** 174.

VERHAART, W. J. C., and KENNARD, M. A. (1940) *J. Anat., Lond.*, **74,** 239.

WALL, P. D., RÉMOND, A. G., and DOBSON, R. L. (1952) *Rev. neurol.*, **87,** 164.

WOOLSEY, C. N., and CHANG, H. T. (1948) *Res. Publ. Ass. nerv. ment. Dis.*, **27,** 146.

——, and SETTLAGE, P. H. (1950) *Fed. Proc.*, **9,** 140.

——, ——, MEYER, D. R., SENCER, W., HAMUY, T. P., and TRAVIS, A. M. (1950) *Amer. J. Physiol.*, **163,** 763.

——, ——, ——, ——, ——, —— (1952) *Res. Publ. Ass. nerv. ment. Dis.*, **30,** 238.

ZANCHETTI, A. (1954) *Fed. Proc.*, **13,** 169.

NOTES ON THE CLINICAL FEATURES AND PATHOLOGY OF POST-CONCUSSIONAL VERTIGO, WITH ESPECIAL REFERENCE TO POSITIONAL NYSTAGMUS

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THE most prominent features of the post-concussional syndrome are headache, emotional lability, difficulty in concentration and giddiness. Of these, giddiness in one form or another is a particularly persistent and common feature. Thus, Friedman and his collaborators (1945) describe its occurrence in 50 per cent; Glaser (1937) in 60 per cent; and Linthicum and Rand (1931) in 90 per cent of cases. In some instances, true rotational vertigo occurs of a type suggestive of a labyrinthine lesion. This, however, is far from common and Linthicum and Rand describe it in only 4 of 36 cases. In the majority, the character of the giddiness is ill-defined and is generally described in such terms as unsteadiness, a tendency to fall, wavering of objects, a dazed feeling, or confusion in crowds or traffic.

Its pathology is easy to understand in the minority of subjects in whom there is gross evidence of a labyrinthine injury, often with radiological evidence of a labyrinthine fracture accompanied by severe deafness with loss of the caloric responses. In the majority of cases, however, its pathological mechanism remains obscure. Deafness is usually absent, as emphasized by Mygind (1918), Barré and Greiner (1932) and Bremer (1932). Furthermore, little assistance appears to have been derived from the results of formal tests of vestibular function. Thus, Bremer attributed the vertigo to a vestibular hypo-excitability. On the other hand Barré and Greiner (1932) and Portmann and Despons (1937) found hyper-excitability.

The clinical importance of post-concussional giddiness is derived from its disabling character and the frequency of its occurrence. There is, therefore, an urgent need for some further enquiry into its pathological basis, and this we have been encouraged to undertake by certain recent developments, both in the technique of the tests of vestibular function and in our knowledge of the symptomatology and pathology of organic disorders of the vestibular system. These will be discussed in some detail.

Tests of Vestibular Function

The technique of caloric stimulation, first described in 1942 by Fitzgerald and Hallpike, has since come into increasing use together with the methods proposed by its authors for the recording and interpretation of its results. The method involves the application of standardized stimuli, both cold and hot, of moderate intensity, and the magnitude of the resulting nystagmic responses is expressed in terms of their duration. Statistical studies of the results obtained in normal subjects have been carried out by Hallpike, Harrison and Slater (1951), Petermann (1953) and by Thomsen (1953). The findings exhibit a remarkable degree of uniformity and provide a satisfactory basis for the interpretation of the results obtained in cases of vestibular disease.

In these, two types of abnormality have been found to occur, firstly, a reduction in sensitivity of one or other external canal, a so-called canal paresis; secondly, preponderance of the nystagmic reactions occurring in a particular direction, either to left or right. This is the phenomenon of directional preponderance. The tests are delicate in a quantitative sense, that is to say, they permit the recognition of comparatively small abnormalities. Qualitatively, also, they yield results which are much more penetrating than any obtainable by other methods. The method has been in constant use at the Lincoln County Hospital since 1946. During this time it has been used with satisfactory results on several thousand occasions when an examination of vestibular function was required.

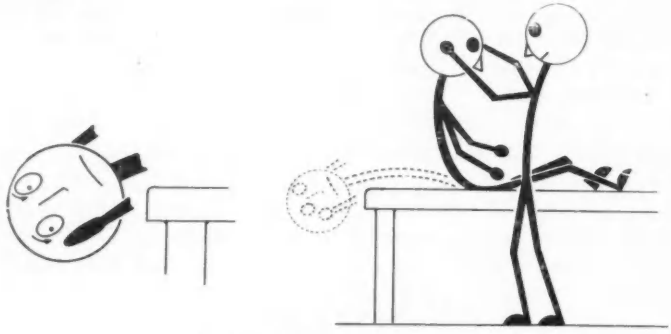
The Symptomatology and Pathology of Organic Vestibular Disorders with Particular Reference to Positional Nystagmus

The occurrence of nystagmus in certain critical positions of the head and its significance as a physical sign of organic disorder of the vestibular system were first clearly described in 1923 by Bárány. The extensive studies of Nylén have since demonstrated that it is due in a proportion of cases to an organic lesion of the cerebellum or other parts of the central nervous system within the posterior fossa.

In a particular variety of the disorder, however, clearly described by Bárány, there did not appear to be any evidence of a lesion of the central nervous system and for this and other reasons he attributed it to a lesion of the otolith apparatus within the labyrinth.

A great deal more is now known of the clinical features and pathology of this condition as a result of the investigations of Dix and Hallpike, of which a detailed account was published in 1952. The patients affected are generally within the age group 40–60 years without preference for sex, and give a characteristic history of a number of attacks of giddiness occurring in certain postures. Routine clinical examination usually

shows no abnormal physical signs, either in the ears, nose and throat, or the central nervous system. The diagnosis, therefore, depends upon the demonstration of vertigo and nystagmus when the head is placed in certain critical positions. The correct procedure for eliciting results and the character of the nystagmus is shown diagrammatically in the accompanying figure.



Method of eliciting nystagmus.

The patient is first seated on a couch with his head turned to one side or the other and then brought back quite rapidly over the end of the couch. Nystagmus and associated vertigo may come on almost at once, but there may be a delay of several seconds. The patient usually shows signs of distress and may close his eyes and try to sit upright. Usually, however, there is no difficulty in persuading him to remain in the test position and the nystagmus can then be observed. It is usually rotational with a horizontal element. The rapid component of the nystagmus is directed towards the under ear, the nystagmus increases rapidly and then dies away, usually within a minute or so with relief of vertigo. On sitting up there may be a brief burst of nystagmus, opposed in direction to that observed in the supine position. On repetition the nystagmic response is characteristically reduced and may be abolished altogether. It may then be impossible to evoke it again without an interval of rest.

The paroxysmal character of the nystagmus, taken in conjunction with the absence of any evidence of a progressive lesion in the central nervous system or elsewhere, together with the natural history of the disorder led Dix and Hallpike to apply to it the descriptive term of "positional nystagmus of the benign paroxysmal type." Their explanation of its pathology was primarily clinical. In a significant proportion of cases, evidence of ear disease was present. This took the form, either of a middle-ear infection, or of some abnormality in the caloric test responses. In a number of such cases, the ear disease was unilateral and in these it was found that the nystagmus was regularly directed towards the affected

ear when this was beneath. From these, and other data, it was thus concluded that the nystagmus was an irritative phenomenon arising from a lesion, infective, traumatic or vascular, of the otolith system, towards which when undermost, nystagmus was directed. This conclusion was supported by a detailed histological examination of the labyrinth in a characteristic case. Dix and Hallpike stated that in a further number of their cases the lesion appeared to be associated with foci of infection in the nose and throat. In others there was evidence of labyrinthine trauma.

Gordon (1954), too, in a recent paper stresses the occurrence of the benign paroxysmal type of positional nystagmus as a sequela of head injury and its relevance to the present investigation, therefore, needs no further emphasis.

The clinical features of the other type of positional nystagmus which, as shown by Nylén, may accompany cerebellar and other lesions within the posterior fossa, do not yet appear to have been subjected to any detailed analysis. It seems clear, however, from the writings of Nylén and others that in this so-called "central" type, the features so characteristic of the benign paroxysmal type of positional nystagmus are not so much in evidence. That is to say, the nystagmus is much more persistent and may often be unaccompanied by severe vertigo. As emphasized by Gordon, this variety of positional nystagmus may also occur as a sequel of head injury, presumably as the result of cerebellar lesions.

Present Investigation

In this, two different approaches have been made to the problem. Firstly, a study has been made of the characteristics of positional nystagmus as seen in a consecutive series of 123 subjects found to exhibit this phenomenon, together with an analysis of the associated clinical features and the possible ætiological factors concerned, with particular reference to head injury.

Secondly, the vestibular signs and symptoms observed in a consecutive series of 108 subjects admitted because of head injury to a particular hospital have been analysed. Here again, particular attention has been directed towards the frequency of occurrence and characteristics of the phenomenon of positional nystagmus.

Part I.—The Clinical Features of Positional Nystagmus

Material.—The case notes of 123 consecutive cases of positional nystagmus were reviewed. The majority of patients were seen at the Out-patient Departments of the Lincoln County and Grimsby General Hospitals. In 104 the positional nystagmus was of the benign paroxysmal type, as defined by Dix and Hallpike. Sex and age distribution was as follows: Males 57, females 47.

Age	0–20	21–30	31–40	41–50	51–60	61–70	+70
	1	4	16	31	33	18	1

In 90 of the 104 patients the chief complaint was of rotational vertigo and in 71 of these the symptoms had been noticed in bed, particularly when turning over. In none of the cases was there present any abnormal neurological sign or symptom apart from the eighth nerve system. In 58 some evidence of local ear disease was found and in 15 an obvious infective process was present, tonsillitis, dental sepsis, sinusitis, syphilis or tuberculosis.

The role of ear disease in the causation of positional nystagmus.—The otological abnormalities in the 58 subjects with evidence of ear disease are tabulated as follows:

	No of cases
Otitis media in ear placed beneath in test position	7
Caloric abnormality only in under ear	28
Caloric abnormality with deafness in under ear	8
Deafness with no other evidence of an aural lesion	15

In 5 other subjects the only aural abnormality was an abnormal caloric response in the uppermost ear, while in 16 other cases the caloric responses, though abnormal, were symmetrical.

It will be seen that, of the 58 subjects with evidence of aural disease, the disease appeared to be unilateral in 48. In 43 of these the affected ear was that placed undermost in the test position. These findings appear to be in very good accord with those of Dix and Hallpike, who found that, of 24 cases with substantial evidence of unilateral ear disease, the positional nystagmus was directed towards the affected ear, when placed beneath, in no less than 21.

The role of head injury in the causation of positional nystagmus.—In 19 of the 104 cases (18·2 per cent) exhibiting positional nystagmus of the benign paroxysmal type, a clear history of head injury was given. As with epilepsy of late onset the possible causal significance of antecedent head injury is often difficult to evaluate, and in these 19 cases the circumstances connecting the injury with the subsequent vertigo have, therefore, been considered with some care.

Eleven of the patients were admitted to hospital with the head injury, 9 were unconscious, but in 2 it was not possible to say if unconsciousness had occurred. Fourteen patients volunteered head injury as the cause of the vertigo and one other patient associated head injury with the onset of the vertigo. Symptoms were present almost immediately after the injury in 12 patients, in one after a week, in another after seven weeks, another four months and in 4 others after twenty months, two years, eight years and thirteen years respectively. The patient whose vertigo developed eight years after the head injury associated the symptom with the accident, but the other 3 with periods over twenty months or more between accident and symptons did not associate the two.

Four patients developed the vertigo whilst still in-patients after the head

injury, 6 attended the out-patient department within three months of the onset of the vertigo, 2 others within six months and 5 others in two years (2), twenty years, twenty-nine years and thirty years after the onset of the vertigo.

Seven patients were shown by X-rays to have fractures of the skull, 3 of the occipital bone, 3 of the base of the skull involving the temporal bone, and 1 of the base and vault of the skull. In 5 cases no evidence of fracture was found radiologically and in the remaining 7 cases X-rays were considered unnecessary.

After careful study of these 19 cases it seemed justifiable to accept head injury as a significant factor in the causation of the positional nystagmus. In a large percentage the onset of the vertigo followed the head injury sufficiently closely for the association to be obvious. In the remaining cases the head injury appeared the important ætiological factor in the history, and no other cause for the nystagmus was found in history or detailed examination.

The clinical features of these post-traumatic cases were, in every other respect, indistinguishable from those of the other members of the group.

In the remaining 19 of the 123 subjects of the series, the character of the positional nystagmus was more in keeping with that of the so-called central type, being more persistent and accompanied by little vertigo. In one of these cases the diagnosis of disseminated sclerosis was made. In the others no definite evidence of the site or nature of the lesions was obtainable. In none, however, was there any evidence of head injury as a causal factor. In none, also, was there any otoscopic evidence of ear disease. Moderate degrees of hearing loss were present in 4 cases. In 3 this was bilateral and in 1 unilateral. Unexplained caloric abnormalities were present in 5 cases.

Part 2.—The Occurrence of Positional Nystagmus in a Series of Cases of Head Injury

In this part of the investigation, systematic observations for positional nystagmus were carried out upon 108 consecutive cases of head injury admitted to one general hospital. In nearly all some complaint was made of dizziness. As already stated, much doubt and confusion exist concerning the pathological basis of this symptom and in the present investigation our chief endeavour has been to ascertain the extent to which it could be attributed to organic disorder of the otolith apparatus, as shown by the occurrence of positional nystagmus or vertigo of the benign paroxysmal type.

Results.—These are stated briefly as follows:

Age distribution of all fracture cases:

Age	0–20	21–30	31–40	41–50	51–60	61–70	+70
	38	16	22	14	7	6	5

Occurrence of positional nystagmus.—Seventeen of the 108 subjects (15 per cent) exhibited characteristic positional nystagmus of the benign paroxysmal type to one side or the other when first seen within fourteen days of the head injury. Here the age distribution was as follows:

Age	0–20	21–30	31–40	41–50	51–60	61–70	+70
	4	6	3	—	1	2	1

Occurrence and character of dizziness apart from positional nystagmus.—Although, as stated, some complaint of dizziness was made by nearly all of the 108 subjects, a rotational element was a feature of this dizziness in only 3 of the 91 cases without positional nystagmus, while it was present and marked in 15 of the 17 cases with it.

Occurrence and significance of skull fractures.—In a number of the cases skull fractures were present, but in none was the labyrinth involved. In the present series, therefore, neither the occurrence of this kind of fracture nor the length of the period of amnesia appear to be related to the occurrence of positional nystagmus.

Caloric test results.—In most of the subjects with positional nystagmus the caloric responses have been abnormal. In some cases the character of the abnormality was indicative of a lesion of the labyrinth placed underneath in the test position. In others, however, the upper labyrinth has been implicated. The significance of this is difficult to explain. According to the findings of Dix and Hallpike the otolithic lesion responsible for the positional nystagmus is located in the under labyrinth and this might be taken to warrant the expectation that the same labyrinth would also be implicated by an abnormality of the caloric responses when this was present.

It must, however, be borne in mind that, as Dix and Hallpike have themselves shown, caloric abnormalities are by no means constantly present in cases of positional nystagmus: furthermore, that the vestibular injuries which result from head trauma are likely from its nature to be widespread and may involve both labyrinths. In this way positional nystagmus resulting from a lesion of the otolith apparatus of the under labyrinth without alteration of its caloric responses might well occur in conjunction with a lesion of the canal organs of the upper labyrinth with alteration of its caloric responses.

Prognosis

The period of recovery from dizziness appears to be dependent to an important extent upon the occurrence or otherwise of positional nystagmus. When this was absent, the recovery period averaged two and a half months. Five of the 17 patients with positional nystagmus, however, continued to exhibit this symptom, though with diminished severity, for more than twelve months. These findings, taken in conjunction with the observations of the duration of the positional nystagmus following head

injury in 19 subjects in our first group indicate that the symptom, if still present twelve months after a head injury, is likely to persist for a considerable time.

Summary and Comments

(1) In 104 of 123 consecutive cases (84·5 per cent) of positional nystagmus, the nystagmus was of the so-called benign paroxysmal type, as defined by Dix and Hallpike, and due in all probability to a lesion of the otolith apparatus. In 19 of these 104 cases (18·2 per cent) the condition appeared to be a clearly defined sequel of head injury. Head injury did *not* appear to be a causal factor in any of the 19 other cases of the series in which the positional nystagmus was of the so-called central type.

(2) In the large majority of a consecutive series of 108 subjects admitted to hospital with concussion following head injury without serious skull fracture, some form of dizziness was present. In 91 of these the dizziness was slight and without any well-marked rotational features. The average recovery period was two and a half months. In 17 subjects (15 per cent) positional nystagmus of the benign paroxysmal type was present and in these a rotational type of dizziness was complained of. The prognosis of this type of dizziness appears to be more serious and in a number of cases the recovery period was found to exceed twelve months.

(3) In none of the 121 cases of positional nystagmus of the benign paroxysmal type, which have been included in this communication, was there any evidence of an organic lesion of the central nervous system.

Our findings therefore indicate that serious persistent dizziness following head injuries, not necessarily associated with skull fracture, is very frequently, particularly when it is of a rotational character, due to traumatic lesions of the otolithic apparatus. The diagnosis is dependent upon the demonstration of a particular type of positional nystagmus by means of a simple clinical test. Though the lesion is essentially a benign one, the severe nature of the symptoms to which it gives rise is often a cause of severe distress, in particular when its cause is left unexplained. The medico-legal implications of these findings would appear to be considerable. Positional nystagmus as stressed by Gordon (1954) may be a serious cause of incapacity for work following a head injury. If it passes unrecognized, the organic basis of the patient's symptoms will be overlooked and proper recognition of a claim to compensation might unjustly be refused. Such a course of events may bring about severe neurotic sequelae. Thus the importance of early and accurate diagnosis, nearly always quite an easy one, cannot be exaggerated.

REFERENCES

BARRÉ, J. A., and GREINER, G. (1932) *Rev. Oto-Neuro-Ophtal.*, **10**, 633.

BREMER, F., COPPEZ, H., HICGUET, G., and MARTIN, P. (1932) *Rev. Oto-Neuro-Ophtal.*, **10**, 161.

DIX, M. R., and HALLPIKE, C. S. (1952) *Proc. R. Soc. Med.*, **45**, 341.

EULER, H. E. (1952) *Arch. Ohr-, Nas.-, u. KehlkHeilk.*, **161**, 336

FRIEDMAN, A. P., BRENNER, C., and DENNY-BROWN, D. (1945) *J. Neurosurg.*, **2**, 36.

GLASER, M. A. (1937) *Ann. Otol., etc., St Louis*, **46**, 387.

GORDON, N. (1954) *Lancet*, **1**, 1216.

GROVE, W. E. (1928) *Arch. Otolaryng., Chicago*, **8**, 249.

HALLPIKE, C. S. (1951) *Proc. IVth Int. Congr. Otolaryng., Lond.*, 1949, **2**, 514.

——, HARRISON, M., and SLATER, E. (1951) *Acta Oto-laryng., Stockh.*, **39**, 151.

LINDSAY, J. R. (1951) *Ann. Otol., etc., St Louis*, **60**, 1134.

LINTHICUM, F. H., and RAND, C. W. (1931) *Arch. Otolaryng., Chicago*, **13**, 785.

MYGIND, S. H. (1918–19) *Acta Oto-laryng., Stockh.*, **1**, 515.

NYLÉN, C. O. (1950) *J. Laryng.*, **64**, 295.

PETERMANN, A. (1953) *Pract. oto-rhino-laryng.*, **15**, 28.

PHILLIPS, D. G. (1945) *J. Neurol. Neurosurg. Psychiat.*, **8**, 79.

PIQUET, J., and DUROT, A. (1951) *Rev. Oto-Neuro-Ophtal.*, **23**, 141.

PORTMANN, G., and DESPONS, J. (1937) *Rev. Laryng., Paris*, **58**, 585.

SCHUSTER, F. P. (1927) *Sthwest. Med.*, **11**, 116.

SYMONDS, C. P. (1942) *Proc. R. Soc. Med.*, **35**, 601.

THOMSEN, K. A. (1953) *Acta Oto-laryng., Stockh.*, Suppl. 109, p. 189.

CERVICAL MYELOPATHY: A COMPLICATION OF CERVICAL SPONDYLOSIS

BY

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With a Surgical Note by L. S. Walsh and Ian Mackenzie

"I am inclined by long observations of spinal affections, to think that the ligaments are more frequently in fault than any of the structures of the spinal column; and that many of the cases of paralysis, whether temporary or permanent, and vaguely classed under functional derangements of the spinal cord, will be found, by dissection, to depend on an altered condition of those textures."
C. ASTON KEY, 1838.

THE effects of acute injury of the cervical spinal cord were known to the Ancient Egyptians (Breasted, 1930, Cases 29 to 33, 48). That chronic trauma due to bony and ligamentous changes also occurs is, despite the foresight of Aston Key (1838), a recent concept and we propose to review this condition in the light of the literature and the experience of 120 cases.

The term "cervical spondylosis" (Schmorl and Junghanns, 1932; Forsberg, 1939) refers to chronic degenerative changes due primarily to intervertebral disc decay (Bailey and Casamajor, 1911; Beadle, 1931; Keyes and Compere, 1932; Horwitz, 1940; Saunders and Inman, 1940; Brain, 1954*a*), which are probably universally present in elderly persons. In many this process is symptomless but occasionally neurological complications—root or cord compression—result. If cord involvement occurs, the clinical picture of cervical spondylotic myelopathy is produced. The term "cervical disc" is usually applied to this condition but as it does not describe the cord lesion and as the disc is only partially responsible for the spondylosis, it should be used no longer. The true incidence of cervical myelopathy is unknown but as Pallis, Jones and Spillane (1954) have shown, mild forms, at time manifest only objectively, may be relatively common.

Cord involvement may also occur as a result of an acute prolapse of the cervical intervertebral disc and it is of great importance to differentiate this from the more chronic cervical myelopathy, especially as the pathology (Brain, 1948; Frykholm, 1951), prognosis and treatment are different. It is

impossible to review cervical myelopathy without considering both diseases because until recently a distinction between the two has been made by only a few authors (Brain, 1948; *Lancet*, 1952) and much confusion in thought and therapy has followed.

History

Although Monro (1771) recognized the function of the disc and Portal (1772) knew of its role in the ageing spine, it did not receive clinical recognition until Ollivier (1824) described bulging of the intervertebral cartilages as a cause of chronic spinal cord compression. However, apart from Key's (1838) cases and short anatomical accounts by Rokitansky (1844), Virchow (1857) and Luschka (1858), and despite Dexler's (1893) report of similar lesions in the dog, the history of cervical spinal cord lesions due to disc disease began only fifty-five years ago. Taylor and Collier (1901, Case 5) and Oppenheim and Krause (1909, Case 3) described patients who came to operation; the first, an example of the acute traumatic type, was operated on by Horsley in 1892 (Walshe, 1951). Oppenheim and Krause (1909) considered the lesion a neoplasm ("enchrondroma") and thereafter apart from occasional cases of disc prolapse in other parts of the spine (Goldthwait, 1911; Middleton and Teacher, 1911; Calvé and Galland, 1922), they were reported as such under various names (Potel and Veaudeau, 1913; Nonne, 1913, Case 5; Steinke, 1918; Veraguth, 1929, Case 17; Bucy, 1930). Stookey (1928) made the first study of "ventral extradural chondromas" which, like those of Adson (1925) and Elsberg (1925) were in the cervical region and treated surgically.

Meanwhile Schmorl (1929) and Andrae (1929) described the anatomical aspects of disc protrusion and although they were unaware of the clinical implications of their work, it rapidly became apparent that spinal cord damage could be associated. Kortzeborn (1930) described one of the first cervical cases on a basis of this new knowledge. Elsberg (1931), Camp, Adson and Shugrue (1933), and Mixter and Barr (1934), Peet and Echols (1934), Mixter and Ayer (1935) and Love and Walsh (1938) dealing mainly with cervical cord damage, and Alajouanine and Petit-Dutaillis (1930) considering similar lesions elsewhere, established as a distinct entity cord compression by a prolapsed disc. Later Stookey (1940) admitted that the tumours he had previously described were of this nature.

The neurological complications of cervical spondylosis were studied separately and except by occasional authors (Bailey and Casamajor, 1911) were not associated with disc disease until recently. Cervical spondylosis had been recognized long before Wenzel (1824) and Lane (1886) described it in detail but Jaccoud (1864), Leyden (1874) and Gowers (1886) were the first to mention cord involvement. Initially there was confusion with ankylosing spondylitis (Kocher, 1896) and some of the authors cited by Epstein and Davidoff (1951) and by Brain, Northfield and Wilkinson (1952) were plainly describing this disease; Osler and Macrae (1910),

on the other hand, were dealing with true spondylosis. The cases of Pastine (1912), Barré (1925), Parker and Adson (1925, Case 2) and Kienböck (1933) were the first to be reported with cervical cord involvement and Christiansen (1924) discussed the problem. However, the role of spondylosis in producing a myelopathy was overshadowed by the acute disc syndrome and only recently has its significance been recognized (Brain *et al.*, 1952; Spillane and Lloyd, 1952).

Many authors (Mixter and Barr, 1934; Kristoff and Odom, 1947; Bucy, Heimburger and Oberhill, 1948; Paillas, Duplay and Bonnal, 1949; Masson and Devic, 1949; Gros and Temple, 1953; Stern and Rand, 1954) have failed to distinguish between the two conditions affecting the cervical disc and their generalizations are therefore of little value. Others have considered only the acute or subacute syndrome (Semmes and Murphey, 1954; MacDonald, Dodge and Clark, 1955) and thus have increased the confusion. Some have dealt with cord and root sequelæ together and their conclusions are equally difficult to assess (Morton, 1936; Brain *et al.*, 1952; Scaglietti, 1953). Reference therefore to the literature of this subject must be undertaken with particular care.

Since 1901, about 330 cases of cervical cord compression due to disc disease of the acute or chronic type have been reported, but only two-thirds in detail. Of these cases 190 are acceptable examples of chronic cervical myelopathy as defined here, although the undetailed series of Stookey (1928), Browder and Watson (1945), Knight (1948), de Vet (1948), Strully, Gross, Schwartzman and von Storch (1951), Thurel (1951) Marinacce (1952–3), Pool (1953), Davis, Odom and Woodhall (1953), and Guillaume and Caron (1954) must have included many genuine cases. During the fifty years from 1901 to 1950, 64 cases appeared in the literature whereas in the last four years there have been 125.

Material

Of the 120 patients comprising this series, 112 had been encountered at the National Hospital, Queen Square. 6 have been recorded in detail elsewhere (Hawk, 1936, Case 6; Mair and Druckman, 1953, 4 cases; Greenfield, 1953); some were included among the spastic paraplegics discussed by Marshall (1955) but it is difficult to ascertain the exact number. 8 patients were observed at Hammersmith Hospital and have been reported already (Clarke, 1955).

Only those patients in whom spinal cord compression due to cervical spondylosis could be demonstrated by myelography, or at operation or autopsy were accepted. Several cases that clinically were almost certainly examples of cervical myelopathy had to be excluded because these criteria had not been satisfied. 2 cases of the acute syndrome were rejected and the patient already described by Taylor and Collier (1901, Case 5) likewise. In the latter, optic neuritis was also present and although an association has

been reported (Paufique, Girard and Étienne, 1950) the case remains under suspicion. In a few cases, the possibility of cord compression due to associated thoracic spondylosis seen on myelography existed and they were therefore excluded.

Ætiology and Pathology

The degenerative process in the cervical spine is the basic ætiological feature of cervical myelopathy. The primary defect is in the disc, which degenerates and promotes osteophyte formation at the periphery of the vertebral body. The posterior osteophytes, with the overlying ligaments, may project into the spinal canal or intervertebral foramina at one or more levels, and in some cases encroach upon nervous tissue.

There are three causative factors of this condition and the commonest is the normal ageing process; it was present in 105 (87·5 per cent) of our cases. The spondylosis so produced may be termed "primary." The other two ætiological factors are the presence of a congenital bony anomaly in the cervical spine and acute trauma to the neck; they produce "secondary" spondylosis and comprised 15 of our cases (12·5 per cent). In each secondary type, degenerative changes take place in an otherwise normal spine at a premature age due to mechanical instability (Brain *et al.*, 1952; Greenfield, 1953). 11 cases (9·2 per cent) had malformations which included fusion of 2 vertebræ in 8 and maldevelopment of laminæ in 3.

In 4 cases (3·3 per cent) acute trauma had precipitated the onset of spondylotic changes which later led to neurological sequelæ. The difference between these subacute cases and the acute disc syndrome, excluded from consideration here, is probably only one of degree. The present cases pursued a more chronic course and were comparable clinically with the cases of myelopathy of other ætiology. They have been included here to indicate their existence, although in the future it may be necessary to exclude them. The pathological changes are similar to those in the acute disc syndrome where the annulus fibrosus is torn and disc material protrudes. The effect of the protruding mass is insufficient at the time of the sudden episode to disturb the function of the spinal cord. The damage to the spinal column leads to progressive spondylotic changes and cord compression of a slower and less catastrophic kind. The course was more chronic in the above-mentioned 4 cases with acute injury to the neck (average duration, fifteen months). Their ages were less than 40 years and each came to operation.

The part played by trauma has caused dispute and varying reports (Bucy *et al.*, 1948; Masson and Devic, 1949; Müller, 1951; Brain *et al.*, 1952), often due to confusion with the acute disc syndrome. Wenzel (1824) and Lane (1886) first noted the effects of chronic occupational trauma on the development of spondylosis and it probably contributed to it in some of our patients with the type due to ageing (Primary). It is also

possible that it may have some part to play in the production of the myelopathy because there seemed to be a higher incidence of the disease amongst those who carried heavy loads on their heads or shoulders and also in dancers and gymnasts. One of our patients had spasmodic torticollis.

The role of acute trauma is more difficult to evaluate but there seem to be at least four possibilities. It may produce the acute disc syndrome, with which we are not concerned; it may induce secondary spondylosis (4 cases mentioned already); it may lead to cord compression in a spondylotic but symptomless spine (Group 3 of Brain *et al.*, 1952); or established cervical myelopathy may be aggravated by it. Acute trauma led to cord damage in 9 of our patients who had had symptomless but spondylotic spines before injury—and in 2 other patients established myelopathy was aggravated by the injury. Including all types, the total in which trauma was indisputable was 15 (12·5 per cent); another 4 had a less definite association and in some others past injury may have been significant but the evidence was not strong enough to justify their inclusion.

There are several factors that appear to be responsible for the cord lesion. Neck movements are obviously important and acute extension is the one most likely to damage the cord (Harbitz, 1939; Taylor and Blackwood, 1948). Michelsen and Mixter (1944), Paillas *et al.* (1949) and Fender (1952) have reported striking examples, and Allen (1952) at operation could invoke blanching of the cord by extending the neck. In the presence of established spondylosis acute neck extension may lead to cord damage (Barnes, 1948; Symonds, 1953; Schneider, Cherry and Pantek, 1954) and this occurred in 4 of our 11 cases in which trauma played a role. The movements of everyday life in a spondylotic spine may also be responsible (Bradford and Spurling, 1945) and even those due to respiration and arterial pulsation have been incriminated (Bucy *et al.*, 1948). The anchoring of the cord by the dentate ligaments helps to potentiate anterior cord compression (Kahn, 1947; Bedford, Bosanquet and Russell, 1952) and the latter combined with posterior pressure due to corrugation of the ligamentum flavum at the same level, is a potent factor (Taylor, 1953; Schneider *et al.*, 1954; Clarke and Little, 1955). Some authors (Girard, 1952; Girard, Garde and Devic, 1954) have considered local arachnoiditis, extradural adhesions (Brain *et al.*, 1952; Taylor, 1953) or direct neuronal damage (Bedford *et al.*, 1952) to be of ætiological significance, and the work of Mair and Druckman (1953) has emphasized the role of the anterior spinal artery in this condition. This vessel is compressed by the spondylotic changes and the regions at the periphery of its territory of supply in the cord suffer ischæmia, a conception that correlates well with the clinical findings. Schneider (1955) has recently drawn attention to the direct involvement of the anterior spinal artery in acute injury to the cervical spine. The reason why only certain individuals with cervical spondylosis develop myelopathy is obscure but the blood supply of the

cord (Bartsch, 1954), ageing of the cord (Bailey, 1953), cord ischæmia due to associated cardiovascular disease (Brain *et al.*, 1952), the relative size of the spinal canal, and the presence of congenital bony anomalies (Clarke and Little, 1955) must all be considered.

Clinical Picture

Cervical myelopathy, although produced by apparently discrete lesions, presents a pleomorphic clinical picture similar to the varied pattern seen with tumours in this region (Meyer and Fine, 1949; Webb, Craig and Kernohan, 1953). Because of the multiplicity of protruding lesions in most cases of cervical spondylosis and the frequent association with root involvement, the picture of cervical myelopathy is even more complex (Brain *et al.*, 1952). In addition, those with single lesions at a given level do not necessarily have a constant pattern.

In all the clinical considerations it has been difficult or impossible to differentiate between sensory phenomena of cord and of root origin in the upper limbs. Müller (1951) reported root features in almost half of his cases. In our experience, however, if one considers motor, sensory and reflex changes, the frequency of root features may be higher and even as much as 90 per cent.

Age

The ages of the patients at the time of diagnosis are shown in fig. 1; the youngest was 35 and the oldest 80. The mean age of 53 years is

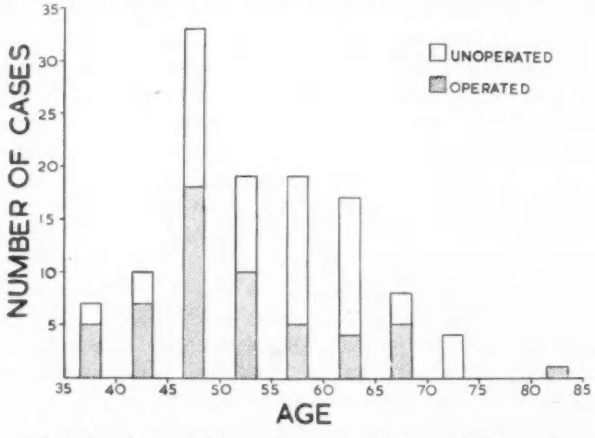

Fig. 1.—Age of 120 patients at the time of diagnosis.

probably fallacious because frail and elderly patients with an apparently satisfactory diagnosis of chronic spinal cord disease are unlikely to be investigated with cervical myelopathy in mind. Furthermore, we excluded

several patients who had the typical clinical features but were too old and incapacitated to tolerate myelography and in whom active treatment was not contemplated. The average age is therefore likely to be higher than we have indicated.

Sex

There were 85 males and 35 females, a ratio of 2·4:1. The predominance of men, which has been frequently confirmed, is presumably related to occupational trauma (Wenzel, 1824; Lane, 1886).

Presenting Complaints

By considering the patient's first symptom, it was possible to delineate 7 distinct groups (Table I); the mean ages of each are given in Table I.

TABLE I.—PRESENTING SYMPTOM GROUPS: THEIR FREQUENCY INITIALLY AND AT THE TIME OF DIAGNOSIS IN 120 CASES

Group	*Symptom*	*Frequency initially* (%)	*Mean age* (*years*)	*Mean duration of disease before diagnosis* (*years*)	*Frequency at time of diagnosis* (%)
I	Motor symptoms in one leg	27·5	53 (35–80)	3½ (3 months to 11½ years)	96
II	Motor symptoms in both legs	22·5	55 (40–70)	3¾ (1 month to 10 years)	
III	Sensory symptoms in arms or hands (excluding pain)	19·2	50 (36–67)	1½ (6 weeks to 4 years)	74
IV	Pain in neck, shoulders or arms	18·3	52 (38–69)	2 (2 months to 15 years)	67
V	Electric shock symptom	5	53 (45–63)	1¾ (6 months to 4 years)	12
VI	Sensory symptoms in legs	4·2	49 (43–67)	3 (6 weeks to 12 years)	20
VII	Motor symptoms in arms	3·3	53 (47–67)	5 (2½ months to 11 years)	68

No connexion between the mode of onset and the age of the patients could be discovered and the conclusions of Brain *et al.* (1952), concerning localization of the lesions and the presenting complaints, could not be verified except in the few cases with a single lesion.

Group I: Motor symptoms in one leg.—33 cases (27·5 per cent). The patient's first indication of the disease was trouble with one leg, usually weakness with or without stiffness, but on rare occasions stiffness alone. In only a few cases were paræsthesiæ also present in the affected limb. Distal weakness was commonest and a typical complaint was of dragging the foot. Neck and sphincter symptoms were no more common in this

group than in the whole series. As the disease progressed, usually at a slow rate, weakness of the contralateral leg or the ipsilateral arm or sensory phenomena in the limbs followed.

Group II: Motor symptoms in both legs.—27 cases (22·4 per cent). These patients first observed a weakness, with or without stiffness, in the lower extremities which appeared simultaneously in both limbs. 3, in addition, had paræsthesiæ in the fingers and associated sensory features in the legs occurred once. In almost two-thirds of the cases, the weakness was asymmetrical. Bladder symptoms, present in almost one-third, appeared early in the disease and half had neck symptoms at some time. The next symptom was most frequently the appearance of sensory symptoms or weakness in the upper limbs.

Group III: Sensory symptoms in arms or hands.—23 cases (19·2 per cent). Sensory symptoms, which included paræsthesiæ and dysæsthesiæ but not pain, in one or both hands or, less commonly, elsewhere in the upper limb, were the initial symptoms of these patients. Not infrequently, the paræsthesiæ were transient and accompanied at times by root pain, which as a presenting symptom is included in the next group. A generalized, rather than a focal, distribution was commoner; when focal, the ulnar fingers were most frequently involved. Bladder symptoms were less common in this group, being present in only one-quarter. The disease progressed by an extension of the sensory disorder to all of the hand, or to other parts of the same side of the body, and ipsilateral leg weakness might follow.

The clinical picture in these patients appeared to proceed at a faster pace than in the previous groups (Table I) and the average age was slightly less. Progression to a state of severe paraplegia as in Groups I and II was not observed.

Group IV: Pain in neck, shoulder or arms.—22 cases (18·3 per cent). Here are included the patients with neck stiffness or with pain in the neck, shoulders or arms as their first symptom. In most cases the symptoms were of root origin and were either transient or recurrent but more often they persisted. Spinal cord involvement followed soon in all cases but leg symptoms were less severe than in Groups I and II. 4 cases were of traumatic origin, in 2 of which cord compression had been added to a pre-existing root syndrome.

Group V: Electric shock symptom.—6 cases (5 per cent). In these patients the disease was ushered in by the electric shock symptom produced by neck movement. Using the criteria of Lhermitte, Bollak and Nicolas (1924), only those with pure cord involvement were accepted and similar sensations of root origin excluded.

Group VI: Sensory symptoms in legs.—5 cases (4·2 per cent). Here there were paræsthesiæ or dysæsthesiæ of undoubted cervical cord origin in the lower limbs and weakness later developed in the affected leg.

Group VII: Motor symptoms in the arms.—4 cases (3·3 per cent). In these cases there was weakness of one or both upper limbs and in three there was later involvement of the ipsilateral leg.

Clinical Features at Time of Diagnosis

Neck features.—Although the lesion in this kind of myelopathy is by definition in the cervical region, symptoms in the neck were present in only three-quarters of the 120 patients and signs in only a half. This emphasizes the difference between cervical and lumbar disc lesions. Transient pains and stiffness of the neck are common minor maladies and care had been taken to include only those complaints that appeared significant.

15 patients noted severe neck stiffness. Neck pain alone, with or without extension into the shoulders or arms was seen in 35 cases (29 per cent). Some authors give a higher figure (Müller, 1951—39 per cent), due usually to the inclusion of acute cases. The pain was that of the root syndrome and in 11 it was interscapular in location. Occasionally it extended to the occiput to produce headache but this was never severe and not as common as certain authors have supposed (Raney and Raney, 1948; Overton and Grossman, 1952; Kovács, 1955).

Only 11 patients had suffered from an isolated root syndrome previously and in one case it had occurred twenty years before the myelopathy (cf. Case 3 of Müller, 1951). It was moreover unusual for root features to play a prominent part in the ultimate picture in these cases.

The neck was examined in 116 patients and the commonest finding was limitation of movement which was present in 48 (40 per cent); due to stiffness in 31 and pain in 17. All movements were restricted in 12 patients and 3 had almost complete immobility due to severe spondylosis.

Münzer (1935) first reported the electric shock symptom with spondylosis and 15 of our patients had experienced it; in 6 (Group V) it was the presenting complaint. It was usually produced by neck flexion but extension could also invoke it; coughing and sneezing were less common provocative factors. In some cases showing bilateral signs it was unilateral, but it was bilateral in some cases with unilateral signs. It might appear in the legs only, but when it was restricted to one side of the body it affected the side on which there was sensory impairment.

Motor features.—Weakness of the legs was the commonest complaint in this condition and only 5 of our patients were without it at the time of diagnosis. 60 reported it as the first indication of the disease (Groups I and II) and in those with dragging of one foot at the onset, examination then would probably have revealed evidence of bilateral cord disease in most. The 5 patients without motor symptoms in the legs all had pathological reflexes, with or without very mild motor signs. Not infrequently spasticity was greater than weakness and it was often most

easily appreciated when the patient was seen walking. Wasting of the legs was attributed to disuse, or to an associated lumbar disc lesion. 96 patients (80 per cent) were able to walk unaided but 64 of these were restricted to distances varying from 30 yards to 3 miles. There were thus 32 patients (27 per cent) who were unrestricted, including the 5 with no leg symptoms. 19 could walk only with support and most of them were severely disabled. Only 5 (4 per cent) were completely bedridden and in each the history was lengthy (average 10·8 years). Sensation was rarely affected to the same degree, which is the usual finding in cervical cord neoplasms (Tilney and Elsberg, 1926) and bladder symptoms were present in all five.

Although weakness of the upper limbs was the rarest presenting feature (Group VII), 81 patients (67·5 per cent) had it by the time the diagnosis was made. It was never as severe as in the legs and a profound tetraplegia was very rarely seen. Distal weakness, usually of the small muscles of the hands and those of the forearms, was present in 42 (25 bilateral; 17 unilateral) of the 81 cases but was never severe. Wasting was observed in only 14 of these 42 cases. 14 patients had proximal muscle weakness, in 6 of which the weak muscles were wasted; bilateral involvement was commoner. Generalized arm weakness was present in 25 cases (11 bilateral; 14 unilateral) and 6 had wasting (3 bilateral; 3 unilateral). Frequently the motor signs were part of a root lesion of which there was other evidence.

True muscle fasciculation was found in 17 cases (14 per cent). It was present in the upper limbs in each but in the lower in 3. It always appeared in wasted muscles, and in one patient it only followed exercise (Clarke, 1955, Case 1). The proximal musculature of the arms was involved in more than half of the 17 cases, but the small muscles of the hands could be affected alone. The characteristics of the fasciculations did not differ from those classically ascribed to anterior horn cell damage and electromyographic findings in 3 patients indicated a lower motor neurone lesion in each.

Sensory symptoms and signs.—This is the most complex aspect of the clinical picture and Stern and Rand (1954) have recently dealt with it. Our findings agree substantially with theirs, although we would emphasize the frequent and often confusing association of root features and the common occurrence of multiple lesions, thus accounting partially for the complexity of the clinical problem. Sensory findings are much more common than some authors (Kremer and Page, 1951) have suggested.

Sensory complaints are as common in the upper limbs as they are rare in the lower, in contrast to the motor symptoms. If root pain extending to the arm and the electric shock symptom were excluded, 91 patients (76 per cent) experienced sensory phenomena in the upper limbs, of whom two-thirds had it in both. The commonest complaint was of paræsthesiæ,

present in 67 (56 per cent), usually involving the digits, and most commonly the fourth and fifth, the thumb and second digit or the whole hand, with spread occasionally to the forearm; in 6 cases the paræsthesiæ were accompanied by unpleasant dysæsthesiæ. 22 patients had pain as well as paræsthesiæ but only 2 suffered from pain restricted to the arms. In most cases, these symptoms were undoubtedly of root origin but, in some, differentiation from a cord lesion was impossible.

In the legs, root symptoms resulting from disc prolapse in the lumbar region were present in 12 cases. These together with patients who experienced the various sensations that may accompany pure motor weakness, and those with the electric shock symptom are excluded from consideration. 25 patients (21 per cent) had cord sensory symptoms; 7 with ascending, bilateral paræsthesiæ accompanying paraplegia, 7 with posterior column sensation decreased in the weaker or weak leg, and 11 with unilateral spinothalamic sensory symptoms. The latter were associated with weakness of the contralateral leg in 8 patients but in the remainder the weakness was ipsilateral.

Only 2 patients suffered involvement of the trunk and each described a constricting upper abdominal band; sensation was abnormal in this area on examination. 95 (79 per cent) of the patients had abnormalities of sensation at some time before diagnosis. In the remainder, they were discovered later in all but 3 cases where sensory symptoms and signs were both persistently absent.

Cutaneous sensation was affected in the upper limbs of 17 patients and usually involved one or more dermatomes; in 12 it was bilateral. The commonest pattern included the ulnar 2 fingers and border of the hand, with extension to the forearm in some. A posterior column sensory defect was also usually present. A definite bilateral cervical level with involvement of all sensation below it was found in only 3 patients (at C3, C4 and C8 respectively) and in a further 3 it was unilateral; there was asymmetrical sacral sparing in one case. In 8 cases, the sensory level was in the upper thoracic region between T2 and T5 but most often at T3. In another 4 patients this abnormality was associated with cervical dermatome loss and normal sensation between the two. Several authors (Abrahamson and Grossman, 1921; Tilney and Elsberg, 1926; Symonds and Meadows, 1937) have reported this change with extra-medullary cervical cord compressing lesions. Lower thoracic levels (T6 to T10), bilateral in 4 and unilateral in 9, also occurred, the latter usually taking part in a partial Brown-Séquard syndrome. The spinothalamic elements, however, at times appeared in the weaker leg. All except one of the 25 patients with a thoracic level had abnormal features in the arms so that confusion with a thoracic lesion rarely ensued. 3 patients had an asymmetrical "glove and stocking" distribution of sensory deficit associated with affected

posterior column modalities. One patient had isolated, bilateral C2–C5 involvement.

On occasions a dissociation between touch, and pain and temperature was found, which has been said by Tilney and Elsberg (1926) to be frequently present with ventral compression of the spinal cord and does not necessarily imply an intramedullary lesion. Although Spillane and Lloyd (1952) did not find it, posterior column modality defects and motor features were invariably present in these cases.

Joint position sense was defective in half of the patients. It was twice as common for this modality to be more affected in the arms than the legs. Frequently it could be shown that the sole defect was in the little finger.

Two-point discrimination reflected the previous modality, although on occasions the only sensory finding was an impairment of this sensation on one little finger.

Vibration sense impairment was present in half the patients and the commonest finding was diminution in one or both legs, the maximal decrease being in the weaker leg. The arms were alone affected in 6 cases and in the remainder of this group, all limbs. The maximal defect was often in the upper limbs and most marked in the ulnar fingers.

In 18 of these cases postural sense was normal, thus confirming the existence of a dissociation, first noted by Petrén (1910), later by Elsberg (1931) and most recently by Netsky (1953). Brain *et al.* (1952) and Stern and Rand (1954) have also found it in cervical myelopathy.

Reflexes.—The reflexes are of supreme importance in cervical myelopathy because they are invariably abnormal.

The jaw-jerk was examined in 73 patients and in only 5 was it considered brisker than normal. The lesion in these cases tended to be maximal in the upper cervical region (2 at C3–4; 2 at C4–5; 1 at C5–6). Confusion with motor neurone disease had not occurred and in some cases the apparently enhanced reflex was probably normal for the individual. It is to be noted that Bucy *et al.* (1948) described an enhanced jaw-jerk with a C4–5 neurofibroma.

The arm reflexes supplied useful information concerning cord and root lesions. Several patterns were elicited.

(1) Symmetrical increase of arm tendon-jerks, together with an increase of deep reflexes in the legs occurred in about a quarter of the cases. The plantar responses were extensor in all but 8, and the abdominals present in more than half. Differentiation from motor neurone disease was never difficult and in the one patient with an enhanced jaw-jerk the diagnosis of cervical myelopathy was confirmed at autopsy (Mair and Druckman, 1953, Case 3). A significant number of patients in this group had lesions either maximally or singly in the upper cervical cord (C3–4 and C4–5), as would be expected.

(2) Another quarter had brisker reflexes in one arm, and in half of them there was also an asymmetry in the legs, so that they represented the hemiplegic type of clinical picture. In those with asymmetry only in the arms, corresponding motor phenomena did not necessarily exist.

(3) A further third had one or more diminished reflexes in the arms whereas the others, including the finger-jerks, were pathologically brisk. The diminution or absence of one triceps reflex, or of the biceps and radial reflexes bilaterally, with or without some degree of inversion, was the commonest finding. Altogether some degree of inversion of the radial or biceps reflexes was found in 22 cases; there were only five examples of the classical inverted radial reflex.

(4) 13 patients had normal arm, but increased leg, reflexes. The main or only lesion was in the lower cervical cord (C6–7 or C7–T1 in 8 of the 13). Other evidence of arm involvement existed in almost all cases but those without it were difficult to diagnose without myelography.

Abdominal reflexes were absent in 51 cases (42·5 per cent) and brisk and equal in 34 (28 per cent). In the rest they were asymmetrical, often corresponding to the reflex changes of the limbs. They did not necessarily reflect the amount of pyramidal tract involvement in the legs, as suggested by Brain *et al.* (1952).

Leg reflexes were always abnormal and, in the absence of a lumbar disc or severe spasticity, always enhanced.

Sphincter disturbances.—Evaluation of urinary symptoms was difficult because of the age groups with which we were dealing. As far as possible local bladder disorders were excluded, as well as the effect of co-existing lumbar or thoracic spondylosis. The frequency of urinary disturbance in this disease has been variously reported by different authors. Browder and Watson (1945) considered it common yet others (Bucy *et al.*, 1948; Spillane and Lloyd, 1951; Brain *et al.*, 1952) thought it rare. Müller (1951), however, found an incidence similar to ours.

40 per cent of all our patients had bladder symptoms, but they were never a presenting complaint and very rarely severe. Urgency and hesitancy were commonest, frequency and incontinence less common, and retention occurred only once. They appeared at any stage of the disease and usually did not increase in severity. In some they improved or disappeared and in only one did they become disabling.

Bowel complaints, on the other hand, were a noticeable feature in only 3 patients, and again they were never severe. Each of the 3 had fæcal incontinence, and the urinary sphincters were also involved in some degree. Only 1 patient suffered from double incontinence.

Sexual functions have not been assessed.

Miscellaneous features.—A fine, horizontal, *nystagmus*, ill-sustained and in one case transient (Hawk, 1936, Case 6) was found in only 3 patients. It is thus a very uncommon finding, as Booth (1952) has already pointed

out. The level of the lesions did not appear significant and unlike the neoplasms of Webb *et al.* (1953) and others, they were not exclusively in the upper cervical cord. Furthermore, despite involvement of the upper part of the spinal cord in some cases the cerebellar type of clinical picture of Guillain, Bertrand and Garcin (1930) was not encountered.

Horner's syndrome was seen only four times and invariably it was partial, thus substantiating the work of Arieff and Pyzik (1953) who believe that pure cord lesions cannot produce the complete syndrome.

Despite routine testing, the trigeminal sensory loss described by Elvidge and Li (1950) was not found. Dysphagia due to anterior osteophytes (Bauer, 1953; Stephens and Janus, 1954) and pharyngeal paræsthesiæ (Terracol, 1927) were likewise absent, although most patients had been questioned concerning these symptoms. Furthermore the complex and bizarre symptomatology, ascribed by many authors to encroachment upon the vertebral artery canal (Bartsch, Boroffka and Ketz, 1954; Bente, Kretschmer and Schick, 1953; and many others) was never encountered in our patients.

Clinical Groups

In a condition manifesting such clinical complexities, it would seem necessary to provide some form of grouping. Previous attempts to do so have, however, been unsuccessful. Stookey's (1928 and 1940) simple scheme of anterior and anterolateral cord compression is inadequate and a grouping according to the similarity to known diseases of the cord (Thurel, 1951; Gros and Temple, 1953; Guillaume and Caron, 1953; and others) is confusing and unnecessary.

TABLE II.—CLINICAL GROUPS AT TIME OF DIAGNOSIS

1. *Tetraplegia and Triplegia*	
Cases with sensory signs of any kind	45
Cases without sensory signs	8
	53
2. *Paraplegia*	
Cases with root signs in arms (or cord sensory signs)	26
Cases with sensory signs in legs only	10
Cases with sensory level	6
Cases without sensory loss	3
	45
3. *Hemiplegia*	
Cases with Brown-Séquard sensory signs (partial or reverse) ...	13
Cases without sensory loss	4
	17
4. *No leg motor signs*	5
	120 cases

In all but 5 cases it has been found possible to group our cases primarily on a basis of the motor features and subdivide each group so obtained according to the sensory impairment (Table II).

Group 1 (Tetraplegia and Triplegia).—This included 53 cases in which there was weakness of all four limbs or of three limbs with reflex changes in the fourth. The tetraplegia was asymmetrical in only 5. Sensory signs were of all types but a defect of posterior column modalities on the weaker side was the commonest finding. Impairment of all forms of sensation in each limb, or up to a level on the trunk, was also frequent.

Group 2 (Paraplegia).—Of the 45 cases in this group 12 were symmetrical. 32 patients (26 + 6) had an abnormality above the lower limbs (Table II). The abnormal signs in the upper limbs were usually of root origin (motor, reflex or sensory) but, as noted already, differentiation between root and cord sensory phenomena was often impossible. Those in Group 2 with sensory impairment in the legs only (10 cases) and those with no objective sensory loss at all (3 cases), together with similar cases in Group 1 (8 cases), almost invariably had sensory symptoms in the neck or arms.

In *Group* 3 (Hemiplegia), a complete Brown-Séquard syndrome was never seen and in 2 it was reversed so that the spinothalamic deficit was on the weaker side.

There were 5 cases (*Group* 4) with no leg weakness or spasticity but they all, like Case 11 of Müller (1951), had reflex changes in the lower limbs and root features in the arms.

As will be pointed out later, when strict criteria were adopted genuine single level lesions were relatively rare and they did not invariably present a distinctive clinical picture. The expected focal findings of motor, reflex and sensory origins were usually found, however, in varying degrees. It is important to note that multiple lesions in part account for the pleomorphic clinical picture (Stern and Rand, 1954).

The Course of the Disease

An overall view of the disorder was derived from consideration of 26 untreated cases and the remaining cases up to the time of treatment. This conception, obtained from the consideration of a group of patients requiring hospital admission, is no doubt prejudiced by the severity of their symptoms and signs and by the rigid criteria employed for the selection of the cases. Bearing this in mind, however, the picture of the untreated disease so obtained is of value.

The duration of the disease before diagnosis ranged from three weeks to fifteen years, with a mean of three years. The maximal survival without treatment was eighteen years (Mair and Druckman, 1953, Case 4). The average survival of 6 fatal, untreated cases was six and two-third years. 5 patients had a history less than three months and 3 of these had suffered acute trauma to pre-existing spondylosis. In the other 2, together with a

few cases with a four months' history, there had been no trauma and although in some the disc lesion was single, no adequate cause other than rapid, non-traumatic disc degeneration with cord compression could be postulated. Age alone did not seem to be closely connected with any particular rate or method of progress of the condition.

Observation of the present group of patients led to the conclusion that the ultimate prognosis in most cases was poor, although progression was often extremely slow or absent and real improvement rare. The patient who had adjusted himself more successfully to his disabilities often regarded himself as improved, and a halt in the progress of the disease was sometimes similarly interpreted. When these possibilities were excluded however, sustained, spontaneous regression was witnessed in only 2 cases. It was never dramatic or extensive, and complete remission to a normal state, as seen, for example, in disseminated sclerosis, was not found. The way in which patients with cervical myelopathy remain in a static condition is a common and well-known event, but appreciation of it is of prime importance when evaluating treatment. On the whole, motor features were more persistent and progressive than sensory, neck, or bladder features which were apt to be more transient. Thus the few patients showing improvement had predominantly sensory complaints.

The natural pattern of the disease seen in the present series comprised three types:

(1) In 75 per cent the disease process appeared to consist of a series of episodes, during which new symptoms and signs appeared. Between these, deterioration occurred in about two-thirds; only 1 case showed some late improvement and 4 experienced a delayed period during which there was no further worsening of their condition. In about a third of this group, the clinical condition remained unchanged between the obvious exacerbations, for periods varying from a few weeks to several years, although after each relapse new symptoms and signs remained.

(2) 20 per cent of the patients showed a slow, steady progression of symptoms and signs from the time of the initial complaint throughout the period of observation. About 1 in 5 showed a very little late improvement.

(3) In 5 per cent of cases there was a rapid onset of symptoms and signs, followed by a long period (up to fourteen years in one case), during which no new features appeared. Ultimately there was some deterioration which brought the patient under observation.

Since the beginning of this study it has been possible to follow cases not included in the present series. We have seen patients with few symptoms and signs continue for several years without deterioration. These would be classified in Group 3 above and it seems likely that they form a larger group than the present study would indicate, a conclusion implicit in the observations of Pallis, Jones and Spillane (1954).

There were 12 deaths in this series (10 per cent). Only half, however, were due to the disease itself and these patients usually died of pulmonary or urinary infection. Death in the remainder was due to unrelated causes, the disease having been present for ten or more years in 4 cases; one such patient survived eighteen years.

INVESTIGATIONS

Cerebrospinal Fluid

The cerebrospinal fluid (C.S.F.) was examined in every case.

Physical properties.—The pressure and colour were normal.

Manometry.—27 patients had a manometric block. In 2 it was complete, the neck being in a neutral position; myelographic verification was possible in each case. 15 had a partial block without neck positioning and in 12 the myelogram showed a hold-up, partial in 6 and complete in 6. A complete manometric block could be produced in 10 patients by employing "postural manometry." This was carried out with the patient in the lateral position, by application of bilateral jugular compression when the neck was successively in the neutral, flexed and extended position. In this last position a block indicated a space-occupying lesion in the cervical canal (Morton, 1936; Kaplan and Kennedy, 1950; Epstein and Davidoff, 1951, Case 2; Bang, 1955). In each case a hold-up of the myodil column was seen at myelography when the neck was extended. These were the only cases in which "postural manometry" had been employed, thus indicating its diagnostic value, although Spillane and Lloyd (1951) were not impressed.

It was seldom possible to make a correlation between the degree of block and the clinical history in any of these types of cases.

Cells.—A pleocytosis in cervical myelopathy is extremely uncommon and in only 3 cases did the white cells exceed 5 per c.c. (7, 7 and 18 lymphocytes), in the absence of blood.

Protein.—Five fluids were excluded because of blood contamination and of the remainder 67 (56 per cent) were normal (40–50 mg. per 100 ml.). Only 3 exceeded 100 and the highest was 120 mg. per 100 ml. In the 2 cases with a complete manometric block the levels were 50 and 80 mg. per 100 ml. and in those with a partial block an increase was found in half. Likewise only 4 of the 10 patients with a postural block had an abnormal protein content. The lack of correlation between the C.S.F. protein and the clinical picture, as well as the manometric block, suggested that it was an unreliable finding.

Other constituents.—The Lange curve was never abnormal and the electrolytes when estimated were invariably normal.

Radiological Features

Plain X-rays of the cervical spine were available for inspection in 112 of our cases; the reports on the remainder were insufficient for our pur-

pose. There were abnormalities in each, ranging from evidence of mild disc degeneration at a single level to severe and widespread disorganization and ankylosis. The distribution by levels of the bony changes corresponded to those in persons without cord damage (Kuhlendahl and Kunert, 1954, Table III) except that in common with Brain *et al.* (1952) we found the incidence greater at upper cervical levels probably due in part to the frequency of congenital lesions in this region. There seemed to be no strict correlation between the severity of the radiological changes at the time of diagnosis and either the degree or the duration of spinal cord disorder, but no inferences can be drawn from the simple X-rays alone. Stookey (1928), Browder and Watson (1945), Mixter and Ayer (1935), Bucy *et al.* (1948) and others have reported normal radiological appearances but they were presumably dealing with the acute disc syndrome.

Myelography is the most important single investigation, and in the present state of our knowledge must be done whenever possible. It was carried out in 117 cases, using the technique of Davies (1951) and only once did clinical deterioration follow (*see also* Epstein and Davidoff, 1951, Case 1). The total number of lesions at each level is shown in fig. 2.

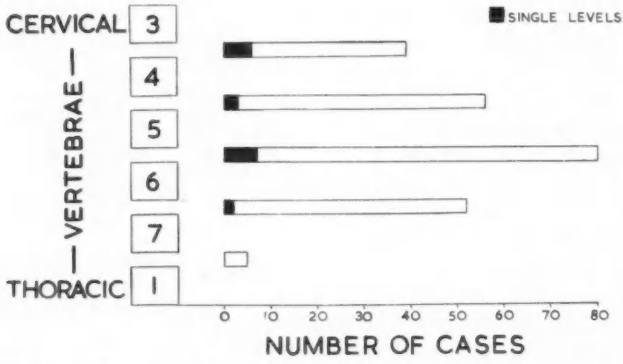

FIG. 2.—Distribution of lesions as shown by myelogram in 117 patients and by autopsy in 3.

There was a hold-up in the opaque material in 39 cases (32·5 per cent). 24 had been forecast by spinal manometry although positioning of the head had been applied in only the last 10 consecutive cases of the series. Correlation between myelographic and postural manometric blocks was perfect, whereas it was only 50 per cent correct when the usual technique was used. Other authors (Spillane and Lloyd, 1951) found good correspondence between the degree of spondylosis on the plain films and the amount of spinal canal invasion as shown by the myelogram but, together with Brain *et al.* (1952), we have been unable to substantiate this. Posterior

vertebral osteophytes seen on the lateral X-rays do not necessarily invade the spinal canal but may be confined to the foraminal region and, on the other hand, some degree of canal encroachment may be seen with myelography that had not been previously suspected. To judge the significance of these findings we examined the myelogram films of the cervical region in 25 patients of the same age group in whom the procedure had been carried out for a thoracic or more caudal neoplasm and who, although having radiological evidence of cervical spondylosis, had no symptoms or signs of cord compression. In none was significant indentation of the opaque column observed.

Single levels.—In 23 cases the plain X-rays seemed to indicate a single lesion, but in some of these myelography revealed indentations at levels previously unsuspected. Furthermore, in those with a low and complete hold-up, the whole cervical canal could not be examined because cisternal myelography had not been carried out. There were thus only 18 acceptable examples (15 per cent) of solitary lesions, whereas Brain (1954*b*) found them in one-third of his cases. 6 were at C3–4, 3 at C4–5, 7 at C5–6 and 2 at C6–7 (fig. 2), the higher incidence at the upper level again being due to the congenital anomalies.

Differential Diagnosis

This has been considered by several authors (Jager and Moffie, 1949; Strully *et al.*, 1951; Brain *et al.*, 1952; Spillane and Lloyd, 1952) and some indication of the difficulties is shown by the diagnoses that had been suggested in 104 of our cases:

	Cases
Disseminated sclerosis	24
Cervical disc [*sic*]	23
Cervical cord lesion	13
Cervical cord neoplasm	12
Motor neurone disease	11
Syringomyelia	5
Thoracic cord neoplasm	4
Spastic paraplegia	4
Subacute combined degeneration of the cord	3
Cerebral hemisphere lesion, arachnoiditis, hæmatomyelia, cerebellar ataxia and lateral sclerosis	1 each
	104

20 of the 24 diagnoses of "cervical disc" had been made in the last three years.

When the overall clinical picture is surveyed, there should be little confusion with syringomyelia, subacute combined degeneration, motor neurone disease or a thoracic spinal cord neoplasm. In the case of the

first, the dense, dissociated spinothalamic sensory loss is never found in cervical myelopathy, and other differentiating features are the lack of trophic changes, the absence of bulbar signs and the older age in myelopathy. Subacute combined degeneration of the cord is more common in men, as is cervical myelopathy, but symptoms and signs are usually symmetrical; the presence or absence of hæmatological changes solves the problem. Adequate elucidation of sensory symptoms and signs is of great importance in differentiating between motor neurone disease and the myelopathy. The length of history and the presence or absence of bulbar symptoms are also valuable points. Jiménez-Díaz and Obrador (1948) and Liversedge, Hutchinson and Lyons (1953) have discussed this problem. A thoracic cord compressing neoplasm may be considered when an upper thoracic sensory level is produced by a cervical cord lesion. Examination of the arms, especially the reflexes, will, however, reveal the correct localization.

In addition there are three conditions that may present considerable diagnostic difficulties—disseminated sclerosis, pseudo-bulbar palsy and cervical cord neoplasm—even with the aid of the ancillary investigations. Differentiation, firstly, from disseminated sclerosis is important because of the therapeutic and prognostic aspects. McAlpine, Compston and Lumsden (1955) and McAlpine (1955) have dealt with this and Barraquer-Bordas and Segarra-Obiol (1952) and McAlpine (1954) have reported cases of disseminated sclerosis that closely simulated cervical myelopathy. The age, mental state, nystagmus, jaw-jerk, severity of sphincter disturbance, muscle wasting, the progress of the disease and the fact that spontaneous complete recovery never takes place in the myelopathy are valuable differential points. In contrast, it must be noted that one or more arm reflexes may be absent or diminished in disseminated sclerosis, as well as in cervical myelopathy and that focal paræsthesiæ may be found in either. It has usually been considered that these two features occur only in myelopathy but this is not so. However, whereas the abnormalities of sensation usually develop slowly and are more extensive in the myelopathy, in disseminated sclerosis they appear more rapidly. The electric shock symptom and the inverted radial reflex both occur in the two diseases. As each is common in this country, association of them may be expected and does in fact exist (McAlpine *et al.*, 1955). Two cases were excluded from the present series because follow-up revealed evidence of both, and it is not impossible that other instances remain.

The second disease that has caused confusion is a type of pseudo-bulbar palsy beginning with spastic leg weakness followed by less severe arm involvement and eventually pseudo-bulbar signs. 4 cases with a confident clinical and myelographic diagnosis of cervical myelopathy had to be excluded when follow-up revealed involvement above the spinal cord. That the two conditions co-existed is possible and, although Webb

et al. (1953) have described bulbar features with cervical cord neoplasms and Rouqués, David and Sors (1951) and Portugal (1943) reported similar cases, it seems unlikely that the whole clinical picture could be due to spondylosis.

Thirdly, a cervical cord neoplasm may simulate the clinical and C.S.F. picture of cervical myelopathy although differentiation by myelography can be readily made. The helpful distinguishing points are that with the neoplasm pain is more frequent (93 per cent—Craig and Shelden, 1940) and it increases with progression of the disease, sphincteric disturbances are commoner, tetraplegia is more frequent—as is the Brown-Séquard syndrome (Broager, 1944)—and the C.S.F. protein is more often increased in amount. In chronic cervical myelopathy the lesion is more likely to be incomplete and at several segmental levels (Brain *et al.*, 1952).

The most important diagnostic features of cervical myelopathy appear to be as follows. The onset, most often with leg weakness, is gradual, at about the age of 50, and the disease is commoner in men, especially those exposed to chronic occupational neck trauma. Progression is often very slow, and physical signs indicate a mixture of cervical cord and root lesions. The reflexes and motor functions are invariably abnormal, and there is almost always subjective or objective evidence of sensory impairment. Cervical spine X-rays show spondylosis and the C.S.F. protein very rarely exceeds 100 mg. per 100 ml. "Postural manometry" reveals a block in many cases and myelography provides verification of the diagnosis.

The acute prolapsed intervertebral disc, with or without trauma, can usually be differentiated: the patient is younger, the onset is often associated with trauma, progress is usually rapid and surgery, which is always necessary, reveals a soft, removable lesion confined to one level. At times, however, the similarities may be many, for an acute lesion may not demand immediate surgery and a subacute state closely simulating chronic myelopathy results. On the other hand, acute episodes, with or without trauma, may take place in a patient with chronic cord compression.

Treatment

Assessment of treatment in chronic cervical myelopathy is difficult for the following reasons:

(1) In a case with root and cord features bed-rest tends to ameliorate the former, whereas spastic leg weakness, if long-standing, may be increased.

(2) Several patients, having been regarded as suffering from an incurable disease, improved because of the interest and hope shown them, although the basic lesion did not change.

(3) A limitation in exercise or stopping heavy work without any specific therapy has been beneficial in some patients, as Brain *et al.* (1952) observed.

Return to work was not a reliable criterion of improvement because those that were deteriorating could often continue their work if light,

whereas heavy workers, even if improved, usually had to seek a more sedentary occupation.

(4) A period of inactivity, varying in duration, is a common characteristic of the untreated disease.

(5) Owing to selection, a relative appraisal of each form of therapy has not been possible in this series.

We have therefore been able to make only a general survey of the results of therapy. On the whole they have been disappointing, and no patient has been returned to a normal healthy state. Of the 120 patients, 54 were operated upon, 37 received no treatment and 29 were treated medically. 8 of the untreated died and 3 could not be traced. The remaining 26, a highly selected group, have been considered when the course of the disease was discussed. Of the 54 operated cases, none was referred for surgery because of the failure of medical therapy, although in many cases the latter had not been given an adequate trial.

Medical Treatment

Medical measures have occasionally been neglected (Semmes and Murphey, 1954; Yuhl, Hanna, Rasmussen and Richter, 1955; Arnold, 1955) but their consideration is of great importance and their neglect implies, even now, a widespread lack of knowledge of the natural history of the disease. Furthermore, the immediate resort to surgery indicates a confusion between the chronic myelopathy secondary to spondylosis and the acute prolapse of the cervical intervertebral disc.

Of the 29 patients of this series who had medical treatment, 1 died and 3 could not be traced, leaving 25 in whom the follow-up period varied from three months to five and a half years, with a mean of two years. Three methods of treatment have been employed.

(1) *Immobilization of the neck* by a collar was carried out in 22 patients, but 5 had bed-rest in addition, and one had neck traction also. Of the remaining 16 patients who had neck immobilization alone, 8 showed improvement. In 4 there was either some improvement in walking, increased ability to dress, or relief of root symptoms in the arms. In 2 there was more striking improvement, as in a man of 50, who had a six months' history of weakness of the legs and numb, weak hands. He had a moderately severe spastic paraplegia, with weak hands and dissociated sensory impairment on the left side of the body. After eighteen months' use of a collar he was walking more easily, and there was then no weakness or cutaneous sensory loss in the hands. The change in 2 was due to general rehabilitation as much as to the collar. Where improvement occurred, it was mainly in the relief of root and electric shock symptoms, but increase in power of the legs was less striking. 8 patients noticed no improvement in their condition, but none was made worse. Of the 6 patients treated

with bed-rest or traction as well as a collar, improvement took place in all, but it was never more than that seen with a collar alone.

The light-frame type of collar was found to be the most effective yet comfortable, and either this or a plastic one was worn during the day. Occasionally a sorbo-rubber support was suggested for use in bed, although the daytime appliance is probably adequate. Trial periods varied from a few weeks to two and a half years. In the latter instance, the patient's initial improvement was not maintained by this prolonged period of neck immobilization.

(2) *Bed-rest*, and (3) *neck traction* could not be adequately evaluated. The former appeared to help root symptoms in the arms, and may ameliorate early spastic weakness in the legs, but it is probably contra-indicated when the weakness of the legs has been present a long time. The results in 3 patients who had neck traction were equivocal, and Brain (1954*b*) found it to be of dubious value.

On the whole, factors such as age, length and course of the illness and severity of the cervical lesion, as judged by the plain films or the myelogram, were not criteria that could be used to predict the possible outcome of medical treatment.

Surgical Treatment—by L. S. Walsh and Ian Mackenzie

Contributions to the surgical approach to cervical myelopathy are few. Kahn (1947) has pointed out the role of the dentate ligaments in cord compression and most surgeons now agree that they should be sectioned in cases of myelopathy. Doubt is expressed by many, however, on the advisability of the more extensive procedure advocated by Allen (1952) where an attempt is made to remove the cord-compressing osteophytes from the anterior wall of the spinal canal.

The group of 32 surgically treated patients, under review here, were under the care of Mr. Wylie McKissock between November 1946 and February 1953. Their ages (fig. 1) and sex incidence corresponded to the findings in the total series.

Four types of operative procedure were used; laminectomy with opening of dura for inspection and subsequent closure (4 cases); laminectomy alone (9 cases); laminectomy with section of dentate ligaments (16 cases); laminectomy with removal of soft disc material (2 cases). One patient died during operation (Mair and Druckman, 1953, Case 1). The 2 patients in whom soft disc material was removed deserve special mention. In one, acute deterioration had occurred in the presence of chronic cervical myelopathy. Operation rather than medical treatment is necessary in such a case, although improvement in our patient was slight. The other case belonged to the group of secondary spondylosis, in which a traumatic incident was followed by a chronic course, although the lesion found at operation simulated that found in the acute disc syndrome.

Results of operation.—Of the 31 survivors, 3 have since died of the disease and 28 have been followed over periods ranging from one and a half to eight years.

5 patients were immediately worse after operation and the 3 subsequent deaths are included here. The operation was thought to be directly responsible for the deterioration. In the case of a woman of 43 the initial symptoms of the illness had been a slow onset of sensory disturbance in one leg and then the other, followed by weakness in all four limbs and pain in the arms. Intradural inspection of the lesion was followed by an increase in arm weakness which improved only on the right side, and a new complaint of central pain in the right leg was now present; seven years later her condition was worse than before operation.

6 patients were worse after operation, but in some this deterioration was delayed, and therefore not directly due to surgical intervention. The operation, however, had not prevented further worsening of the condition.

In 4 patients who ran a steadily progressive downhill course before operation, surgical intervention was followed by an unchanged condition which in one case was observed for eighteen months.

13 patients improved following operation but the change was invariably slight, and its significance difficult to evaluate for the series, considering the widely varying degrees of pre-operative disability. The only patient with a severe disability which improved, remained considerably handicapped. The type of improvement seen in the remainder was exemplified by a woman of 49, who had a slowly progressive history of pain and weakness in the right arm with subsequent weakness of the left leg, which before operation restricted her walking to a few yards. Eight years after operation although still incapacitated, she could now walk one mile.

Relationship of results to various factors.—Although, on the whole, patients under 50 years of age appeared to improve more than the older age groups, neither age nor length of pre-operative history bore any consistent relationship to the outcome of surgical treatment. In common with the medically treated series, the pattern of clinical features, including even a partial or complete manometric block, did not render possible an accurate prediction of the results of surgery. As might have been expected, the chances of improvement were greater in those less severely affected. On the whole, improvement in the arms was more marked than in the legs; similarly, in those patients with subsequent deterioration it had been less marked in the arms. In addition, it is possible for arm features to be ameliorated at the same time as those in the legs became more marked. 5 of the 23 patients, who had all limbs involved, reported that their arms had returned to normal. Considering the type of operation employed, no increase in the proportion of patients improved was seen after section of the dentate ligaments. However, since this routine has been adopted no immediate deterioration has occurred after operation.

Choice of Treatment

Conclusions concerning the significance of age, length of history, clinical picture and course, C.S.F. and myelographic findings were found to be much the same in the medical and surgical groups. These factors do not necessarily help in the selection of treatment nor in a prediction of its outcome.

It is, however, recommended that, in the first place, treatment with a cervical support should be advised. This should be carried out for three months, and if there has been no deterioration the collar should be worn for a further three months. However, at any time, signs of deterioration, or failure to stop a downward clinical course, should demand consideration of surgical treatment without delay, and before the patient is severely disabled. The operation of choice is laminectomy with section of the dentate ligaments. Although we have no information concerning post-operative neck immobilization, further treatment with a collar is probably necessary occasionally, and is recommended by others (Northfield, 1955).

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SUMMARY

(1) Cervical myelopathy is a complication of chronic degenerative changes in the cervical spine (cervical spondylosis) and must be differentiated from the acute intervertebral disc syndrome.

(2) The literature of the condition is reviewed and the clinical picture and radiological and C.S.F. findings are discussed in the light of 120 cases.

(3) Despite the many clinical possibilities a grouping of cases is feasible, according to the presenting symptom, as well as the eventual disease pattern.

(4) The course and differential diagnosis of the disorder are considered and medical and surgical therapy evaluated.

(5) The results of treatment were on the whole disappointing, as far as return to full function was concerned. Where subsequent extension of the disease occurred, it was often very slow. In most cases a trial of neck immobilization is essential, and laminectomy with section of the dentate ligaments if this fails.

REFERENCES

ABRAHAMSON, I., and GROSSMAN, M. (1921) *Trans. Amer. neurol. Ass.*, **47,** 149.
ADSON, A. W. (1925) *Northw. Med., Seattle*, **24,** 309.
ALAJOUANINE, T., and PETIT-DUTAILLIS, D. (1930) *Pr. méd.*, **38,** 1657 and 1749.
ALLEN, K. L. (1952) *J. Neurol. Neurosurg. Psychiat.*, **15,** 20.
ANDRAE, R. (1929) *Beitr. path. Anat.*, **82,** 464.

ARIEFF, A. J., and PYZIK, S. W. (1953) *Arch. Neurol. Psychiat., Chicago*, **70**, 621.
ARNOLD, J. G., Jr. (1955) *Ann. Surg.*, **141**, 872.
BAILEY, A. A. (1953) *Arch. Neurol. Psychiat., Chicago*, **70**, 299.
BAILEY, P., and CASAMAJOR, L. (1911) *J. Nerv. ment. Dis.*, **38**, 588.
BANG, E. DA C. (1955) *Acta Psychiat., Kbh.*, **30**, 1.
BARNES, R. (1948) *J. Bone Jt. Surg.*, **30B**, 234.
BARRAQUER-BORDAS, L., and SEGARRA-OBIOL, J. M. (1952) *Arch. Neuropsiq., S. Paulo*, **10**, 247.
BARRÉ, J. A. (1925) *Paris méd.*, **57**, 266.
BARTSCH, W. (1954) *Nervenarzt*, **25**, 481.
——, BOROFFKA, A., and KETZ, E. (1954) *Acta neuroveg.*, **10**, 214.
BAUER, F. (1953) *J. Laryng.*, **67**, 615.
BEADLE, O. A. (1931) The Intervertebral Discs. Observations on their Normal and Morbid Anatomy in Relation to Certain Spinal Deformities. M.R.C. Special Report No. 161. London.
BEDFORD, P. D., BOSANQUET, F. D., and RUSSELL, W. R. (1952) *Lancet*, **2**, 55.
BENTE, D., KRETSCHMER, M., and SCHICK, C. (1953) *Arch. Psychiat. Nervenkr.*, **190**, 342.
BOOTH, C. B. (1952) *Arch. Neurol. Psychiat., Chicago*, **67**, 69.
BRADFORD, F. K., and SPURLING, R. G. (1945) "The Intervertebral Disc." Springfield, Illinois.
BRAIN, W. R. (1948) *Proc. R. Soc. Med.*, **41**, 509.
—— (1954*a*) *Lancet*, **1**, 687.
—— (1954*b*) *Ann. intern. Med.*, **41**, 439.
——, NORTHFIELD, D., and WILKINSON, M. (1952) *Brain*, **75**, 187.
BREASTED, J. H. (1930) "The Edwin Smith Surgical Papyrus." Chicago, Vol. 1.
BROAGER, B. (1944) *Acta psychiat., Kbh.*, **19**, 45.
BROWDER, J., and WATSON, R. (1945) *N.Y. St. J. Med.*, **45**, 730.
BUCY, P. C. (1930) *J. Amer. med. Ass.*, **94**, 1552.
——, HEIMBURGER, R. F., and OBERHILL, H. R. (1948) *J. Neurosurg.*, **5**, 471.
CALVÉ, J., and GALLAND, M. (1922) *J. Radiol. Électrol.*, **6**, 21
CAMP, J. D., ADSON, A. W., and SHUGRUE, J. J. (1933) *Amer. J. Cancer*, **17**, 348
CHRISTIANSEN, V. (1924) *Ann. Méd.*, **15**, 73.
CLARKE, E. (1955) *Lancet*, **1**, 171.
——, and LITTLE, J. H. (1955) *Neurology*, **5**, 861.
CRAIG, W. M., and SHELDEN, C. H. (1940) *Arch. Neurol. Psychiat., Chicago*, **44**, 1.
DAVIES, H. (1951) *Proc. R. Soc. Med.*, **44**, 881.
DAVIS, C. H., Jr., ODOM, G. J., and WOODHALL, B. (1953) *N.C. med. J.*, **14**, 61.
DEXLER, H. (1893) *Wien. med. Pr.*, **34**, 2040.
ELSBERG, C. A. (1925) "Tumors of the Spinal Cord." London, pp. 195–198.
—— (1931) *Bull. neurol. Inst. N.Y.*, **1**, 350.
ELVIDGE, A. R., and LI, C.-L. (1950) *Arch. Neurol. Psychiat., Chicago*, **63**, 455.
EPSTEIN, J. A., and DAVIDOFF, L. M. (1951) *Surg. Gynec. Obstet.*, **93**, 27.
FENDER, F. A. (1952) *J. Amer. med. Ass.*, **149**, 227.
FORSBERG, R. (1939) *Acta psychiat., Kbh.*, **14**, 325.
FRYKHOLM, R. (1951) Cervical root compression resulting from disc degeneration and root sleeve fibrosis: a clinical investigation, *Acta chir. scand.*, Suppl. **160**.
GIRARD, P. F. (1952) *Rev. Oto-neuro-ophtal.*, **24**, 39.
——, GARDE, A., and DEVIC, M. (1954) *Rev. neurol.*, **90**, 48.
GOLDTHWAIT, J. E. (1911) *Boston med. surg. J.*, **164**, 365.
GOWERS, W. R. (1886) "A Manual of Diseases of the Nervous System." London, Vol. 1, p. 182.
GREENFIELD, J. G. (1953) *Rev. méd. Suisse rom.*, **73**, 227.
GROS, C., and TEMPLE, J. P. (1953) *Sem. Hôp., Paris*, **29**, 1097.

GUILLAIN, G., BERTRAND, I., and GARCIN, R. (1930) *Rev. neurol.*, **2,** 489.
GUILLAUME, J., and CARON, J. P. (1953) *Rev. neurol.*, **88,** 54.
——, —— (1954) *Pr. méd.*, **62,** 1089.
HARBITZ, F. (1939) *Nord. med.*, **1,** 513.
HAWK, W. A. (1936) *Brain*, **59,** 204.
HORWITZ, T. (1940) *Arch. intern. Med.*, **65,** 1178.
JACCOUD, S. (1864) "Etudes de pathogénic et de Sémiotique: les Paraplégies et l'Ataxie du Mouvement." Paris, pp. 222–223.
JAGER, W. A. DEN H., and MOFFIE, D. (1949) *Folia psychiat. neerl.*, **52,** 137.
JIMÉNEZ-DIAZ, C., and OBRADOR, S. (1948) *Rev. clín. esp.*, **28,** 120.
KAHN, E. A. (1947) *J. Neurosurg.*, **4,** 191.
KAPLAN, L., and KENNEDY, F. (1950) *Brain*, **73,** 337.
KEY, C. A. (1838) *Guy's Hosp. Rep.*, **3,** 17.
KEYES, D. C., and COMPERE, E. L. (1932) *J. Bone Jt. Surg.*, **14,** 897.
KIENBÖCK, R. (1933) *Beitr. klin. chir.*, **157,** 449.
KNIGHT, G. C. (1948) *Proc. R. Soc. Med.*, **41,** 511.
KOCHER, T. (1896) *Mitt. Grenzgeb. Med. Chir.*, **1,** 415.
KORTZEBORN, A. (1930) *Zbl. Chir.*, **57,** 2418.
KOVÁCS, Á. (1955) *Acta radiol., Stockh.*, **43,** 1.
KREMER, M., and PAGE, F. (1951) *Arch. Middx. Hosp.*, **1,** 51.
KRISTOFF, F. V., and ODOM, G. L. (1947) *Arch. Surg.*, **54,** 287.
KUHLENDAHL, H., and KUNERT, W. (1954) *Medizinische*, p. 449.
Lancet (1952) Leading article, *Lancet*, **2,** 718.
LANE, W. A. (1886) *Guy's Hosp. Rep.*, **43,** 321.
LEYDEN, E. (1874) "Klinik der Rückenmarks—Krankheiten." Berlin. Band i, pp. 270–278.
LHERMITTE, J., BOLLAK, and NICOLAS, M. (1924) *Rev. neurol.*, **31** (ii), 56.
LIVERSEDGE, L. A., HUTCHINSON, E. C., and LYONS, J. B. (1953) *Lancet*, **2,** 652.
LOVE, J. G., and WALSH, M. N. (1938) *J. Amer. med. Ass.*, **111,** 396.
LUSCHKA, H. (1858) "Die Halbgelenke des menschlichen Körpers." Berlin, p. 144.
MACDONALD, H. N. A., DODGE, H. W. Jr., and CLARK, E. C. (1955) *Proc. Mayo Clin.*, **30,** 154.
MAIR, W. G. P., and DRUCKMAN, R. (1953) *Brain*, **76,** 70.
MARINACCE, G. (1952–3) "Compressions de la moëlle cervicale et affections médullaires non chirurgicales." Thèse de Lyon.
MARSHALL, J. (1955) *Lancet*, **1,** 643.
MASSON, R., and DEVIC, M. (1949) *J. Méd. Lyon.*, **30,** 619 and 705.
MCALPINE, D. (1954) *Arch. Middx. Hosp.*, **4,** 1.
—— (1955) *Lancet*, **1,** 1033.
——, COMPSTON, N. D., and LUMSDEN, C. E. (1955) "Multiple Sclerosis." Edinburgh.
MEYER, B. C., and FINE, B. D. (1949) *Arch. Neurol. Psychiat., Chicago*, **61,** 262.
MICHELSEN, J. J., and MIXTER, W. J. (1944) *New Engl. J. Med.*, **231,** 279.
MIDDLETON, G. S., and TEACHER, J. H. (1911) *Glasg. med. J.*, **76,** 1.
MIXTER, W. J., and AYER, J. B. (1935) *New Engl. J. Med.*, **213,** 385.
——, and BARR, J. S. (1934) *New Engl. J. Med.*, **211,** 210.
MONRO, A. (1771) *Medical Essays and Observations*, **5,** 184.
MORTON, S. A. (1936) *J. Bone Jt. Surg.*, **18,** 893.
MÜLLER, R. (1951) *Acta med. scand.*, **139,** 85.
MÜNZER, F. T. (1935) *Mschr. Psychiat. Neurol.*, **92,** 202.
NETSKY, M. G. (1953) *Arch. Neurol. Psychiat., Chicago*, **70,** 741.
NONNE, M. (1913) *Dtsch. Z. Nervenheilk.*, **47–48,** 436.
NORTHFIELD, D. W. C. (1955) *Brit. med. J.*, **2,** 1474.
OLLIVIER, C. P. (1824) "De la Moëlle Épinière et de ses Maladies." Paris, p. 213.

OPPENHEIM, H., and KRAUSE, F. (1909) *Münch. med. Wschr.*, **56,** 1007, 1077 and 1134.
OSLER, W., and MACRAE, T. (1910) "A System of Medicine." London, Vol. **7,** pp. 201–202.
OVERTON, L. M., and GROSSMAN, J. W. (1952) *J. Bone Jt. Surg.*, **34A,** 155.
PAILLAS, J. E., DUPLAY, J., and BONNAL, J. (1949) *Sem. Hôp., Paris*, **25,** 428.
PALLIS, C., JONES, A. M., and SPILLANE, J. D. (1954) *Brain*, **77,** 274.
PARKER, H. L., and ADSON, A. W. (1925) *Surg. Gynec. Obstet.*, **41,** 1.
PASTINE, C. (1912) *Nouv. Iconogr. Salpêt.*, **25,** 405.
PAUFIQUE, L., GIRARD, P. F., and ÉTIENNE, R. (1950) *Bull. Soc. franç. Ophtal.*, **63,** 90.
PEET, M. M., and ECHOLS, D. H. (1934) *Arch. Neurol. Psychiat., Chicago*, **32,** 924.
PETRÉN, K. (1910) *Arch. Psychiat. Nervenkr.*, **47,** 495.
POOL, J. L. (1953) *Bull. N.Y. Acad. Med.*, **29,** 47.
PORTAL (1772) *Hist. Acad. R. Sci.*, **2,** 468.
PORTUGAL, J. R. (1943) *Rev. bras. Cir.*, **12,** 507. Cited by BUCY *et al.* (1948).
POTEL, G., and VEAUDEAU (1913) *Rev. chir., Paris*, **47,** 713.
RANEY, A. A., and RANEY, R. B. (1948) *Arch. Neurol. Psychiat., Chicago*, **59,** 603.
ROKITANSKY, C. (1844) "Handbuch der pathologischen Anatomie." Wien., Band II, p. 285.
ROUQUÉS, L., DAVID, M., and SORS (1951) *Rev. Neurol.*, **85,** 380.
SAUNDERS, J. B. DE C. M., and INMAN, V. T. (1940) *Arch. Surg.*, **40,** 389.
SCAGLIETTI, O. (1953) *Rev. Chir. orthopéd.*, **39,** 684.
SCHMORL, G. (1929) *Fortschr. Röntgenstr.*, **40,** 629.
——, and JUNGHANNS, H. (1932) Die Gesunde und Kranke Wirbelsäule im Röntgengild: pathologisch-anatomische Untersuchungen. Leipzig.
SCHNEIDER, R. C. (1955) *J. Neurosurg.*, **12,** 95.
——, CHERRY, G., and PANTEK, H. (1954) *J. Neurosurg.*, **11,** 546.
SEMMES, R. E., and MURPHEY, F. (1954) *Surg. Clin. N. Amer.*, **34,** 1095.
SPILLANE, J. D., and LLOYD, G. H. T. (1951) *Lancet*, **2,** 653.
——, —— (1952) *Brain*, **75,** 177.
STEINKE, C. R. (1918) *J. nerv. ment. Dis.*, **47,** 418.
STEPHENS, H., and JANUS, W. L. (1954) *Ann. intern. med.*, **41,** 823.
STERN, W. E., and RAND, R. W. (1954) *Neurology*, **4,** 883.
STOOKEY, B. (1928) *Arch. Neurol. Psychiat., Chicago*, **20,** 275.
—— (1940) *Arch. Surg.*, **40,** 417.
STRULLY, K. J., GROSS, S. W., SCHWARTZMAN, J., and VON STORCH, T. J. C. (1951) *J. Amer. med. Ass.*, **146,** 10.
SYMONDS, C. P. (1953) *Lancet*, **1,** 451.
——, and MEADOWS, S. P. (1937) *Brain*, **60,** 52.
TAYLOR, A. R. (1953) *Lancet*, **1,** 717.
——, and BLACKWOOD, W. (1948) *J. Bone. Jt. Surg.*, **30B,** 245.
TAYLOR, J., and COLLIER, J. (1901) *Brain*, **24,** 532.
TERRACOL, J. (1927) *Arch. int. Laryng.*, **6,** 1025.
THUREL, R. (1951) *Rev. neurol.*, **85,** 536.
TILNEY, F., and ELSBERG, C. A. (1926) *Arch. Neurol. Psychiat., Chicago*, **15,** 444.
VERAGUTH, O. (1929) *Schweiz. med. Wschr.*, **10,** 154.
DE VET, A. C. (1948) *Ned. Tijdschr. Geneesk.*, **92,** 1500.
VIRCHOW, R. (1857) Untersuchungen über die Entwickelung des Schädelgrundes im gesunden und krankhaften Zustande und über den Einfluss derselben auf Schädelform Gesichtsbildung und Gehirnbau. Berlin. p. 53 (footnote).
WALSHE, F. M. R. (1951) *Lancet*, **2,** 1038.
WEBB, J. H., CRAIG, W. M., and KERNOHAN, J. W. (1953) *J. Neurosurg.*, **10,** 360.
WENZEL, C. (1824) "Über die Krankheiten am Rückgrathe." Bamberg.
YUHL, E. T., HANNA, D., RASMUSSEN, T., and RICHTER, R. B. (1955) *Neurology*, **5,** 494.

THROMBOTIC MICROANGIOPATHY (THROMBOTIC THROMBOCYTOPENIC PURPURA) ASSOCIATED WITH ACUTE HÆMORRHAGIC LEUCOENCEPHALITIS AND SENSITIVITY TO OXOPHENARSINE[1]

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THROMBOTIC microangiopathy (TM) is being recognized with increasing frequency: including the one reported here, 99 acceptable cases have been recorded in the literature since the disease was first described by Moschcowitz in 1924 and 1925. References to 85 of these cases are included in a pair of recent papers (Symmers, 1952, 1956): the 14 additional cases were reported by Monroe and Strauss (1953), Heffner, Kahn and Schraft (1954), Rosello, Smith and Arey (1954), Miller and Schaaf (1954), Amick (1954), Stone and Alcott (1954), Lewis and Burger (1955), Ortúzar, Mery and Etchart (1955), Dickenham, Brown, Hiratzka and Vetne (1955), Katz and Jackler (1955) and Wile and Sturgeon (1956). In addition I know of over 30 as yet unpublished cases, including a series of personally studied cases which I hope to describe in a future review. The case of Civin and Gotshalk (1953) may be a further example, bringing the total of published cases up to 100; these authors also mentioned the occurrence in other conditions of lesions more or less resembling those of TM, and the recent paper by Husebye, Stickney and Bennett (1956) is also relevant to this aspect of the subject and particularly to an association with leukæmia which was originally described by Ritama (1954). Bignami's case, referred to in my recent paper (Symmers, 1956) as being "in press", has now been published (Bignami and Germini, 1956). A further review by one of the pioneer students of this disease, the late Dr. Karl Singer, has appeared in Spanish (Singer, 1955). It may be noted, in order to avoid confusion, that the case described by Singer, Bornstein and Wile (1947) was also reported in the transactions of the Chicago Pediatric Society (Wile and Singer, 1948).

When fully developed, the syndrome of TM comprises a diagnostic tetrad of acute febrile illness, haemolytic anaemia, thrombocytopenic

[1] A summary of this paper was read at the session on encephalitis at the Second International Congress of Neuropathology, London, September 12–17, 1955 (Symmers, 1955).

purpura, and neurological disturbances which are often of bizarre and fluctuating type. Disturbances of consciousness are usual; in a few cases psychiatric symptoms have predominated initially, suggesting an acute primary psychosis (Epstein, Deschamps and Chiffelle, 1948; Goldenberg, Thayer and Hastings, 1950; Barondess, 1952; Cooper, Stickney, Pease and Bennett, 1952). Histologically, highly specific lesions of small blood vessels are found throughout the body; in the central nervous system the vasculature of the grey matter is predominantly and even exclusively affected. The illness has been mortal in every reported case, usually within a few days or weeks of the first symptom.

Acute hæmorrhagic leucoencephalitis (AHL), first described by Weston Hurst in 1941, is considerably rarer than TM. Crawford's (1954) review covered 10 cases published under this name, to which may be added 9 more reputed cases (Wolf and Cowen, 1946; Fowler and French, 1949; Csermely and Haberland, 1954—2 cases; Moossy, Wolf and Cowen, 1954—2 cases [one of which is evidently the case reported by Wolf and Cowen, 1946]; Southcott and Fowler, 1954; Lander, 1955; Russell, 1955—2 cases). The disease is doubtless not as rare as these figures suggest: probably some cases have been recorded under names such as "brain purpura" and "hæmorrhagic encephalitis", e.g. some of the cases of Adams, Cammermeyer and Denny-Brown (1949) (*see* Jacob, 1950, *and* Adams and Kubik, 1952). The lesions, which are quite different from those of TM, are confined to the central nervous system, and are wholly or virtually restricted to the white matter. A rapidly fatal course, coma, fits and asymmetrical neurological signs, particularly hemiplegia, are the main clinical features; hæmatological disorders have not been recorded. As in the case of TM there seems to be no important differential age or sex incidence.

Each of these conditions is a disease *sui generis*; there is no prima facie case for supposing that they are in any way related, although ætiological studies have on occasion suggested that hypersensitivity may play a part in the development of each. As the case presented in this paper showed lesions typical of TM in the grey matter of the brain and in the viscera generally, and lesions typical of AHL in the white matter, it is important to stress that the histological lesions of each disease are so characteristic as to be specifically diagnostic, and that there is no likelihood of confusing the one with the other. In order that the case may be seen perspectively a short summary of the pathological findings in TM and in AHL will be given. The photomicrographs illustrating the following account were prepared from this case.

Thrombotic Microangiopathy

The diagnosis of TM depends ultimately on histological demonstration of the highly characteristic lesions which affect arterioles and capillaries,

and occasionally venules, throughout the body. Usually the diagnosis is not confirmed until sections are examined after necropsy; indeed, before definition of the diagnostic symptom-tetrad enabled recognition of the disease during life, the diagnosis of TM remained unsuspected before post-mortem histological examination. The lesions have rarely been demonstrated during life; this is partly due to the small number of cases in which biopsy has been performed, and partly to the relative infrequency of the specific microangiopathic lesions in the tissues which are conventionally chosen for biopsy. As no effective treatment is known, the value of biopsy in this disease is still essentially academic: none the less, early confirmation of the diagnosis should afford opportunities to carry out investigations which may throw light on the nature of TM and on the value of possible therapeutic measures. The potential value of biopsy in TM has recently been reviewed (Symmers, 1956); marrow biopsy may prove to be the procedure of choice.

The vascular lesions are usually most numerous in the myocardium, subcapsular zone of the adrenal cortex, hepatic portal tracts, bone-marrow, kidneys and cerebral grey matter. Blood vessels of the smallest calibre are partially or completely obstructed by granular or hyaline masses, which may extend within the lumen for some distance from a relatively small point of attachment to the wall. The nature of these masses is obscure. It is probable that they develop as platelet thrombi, formed as a result of intimal damage at the site of a focal alteration of the vessel wall, although it has been suggested that at least some of the obstructive masses are protrusions of the altered mural tissue itself. The material within the lumen may retract and become denser, the lumen reopening during this process; endothelium may grow over the mass, which may become organized. Endothelial hyperplasia is sometimes a striking feature, even in vessels which are free from obstructive lesions, and particularly in glomeruli and in the central nervous system. Micro-aneurysmal dilatation of affected vessels is common, and characteristic of the disease. The lesions have none of the features of an angiitis; in particular, serous or fibrinous exudate and cellular exudate do not occur, although an occasional lymphoid cell may be seen in the perivascular tissue around a few lesions. Hæmorrhages may occur around the occluded vessels but often are found apart from them. Ischæmic changes are unobtrusive, in spite of the large number of vessels which may be affected in any organ, sometimes amounting to as many as 90 per cent of the small arterioles and capillaries in vascular tissues such as myocardium and cerebral cortex; microinfarcts or minute foci of parenchymatous cytolysis may be found in severely affected organs, and in the central nervous system focal neuronal damage, glial proliferation and demyelination may occur. The neurological and neuropathological aspects of TM

have been reviewed by Adams, Cammermeyer and Fitzgerald (1948) and Ladwig (1953).

The cause of TM is unknown. The prodomal urticaria and arthralgia of some cases, and the occasional history of infection of the upper respiratory tract a week or two before the acute illness, have suggested that the disease may have an allergic basis. Sensitivity to sulphonamides or other substances has been demonstrated in rare cases. The fibrinoid appearance of some "prethrombotic lesions" of vessel walls in some cases, and observations of features which are associated with disseminated lupus erythematosus, or with polyarteritis nodosa, have suggested a relationship to the so-called "collagen diseases", although this scarcely clarifies the nature of TM itself. The occurrence of hæmolytic anæmia and thrombocytopenic purpura has been thought to support the suggestion that an immunological disturbance may underlie the development of this remarkable disease.

It is certain that more cases of TM would be recognized if this diagnosis were considered in every case in which neurological and hæmatological abnormalities are associated.

Acute Hæmorrhagic Leucoencephalitis

The diagnosis of AHL also depends on histological demonstration of typical lesions (Crawford, 1954). Macroscopically, the appearances are not specific, being those of brain purpura, confined to the white matter and affecting particularly the centrum ovale. Microscopically, the lesions are found practically only in the white matter and are so characteristic as to be diagnostic: they comprise hæmorrhages, perivascular exudates, changes in vessel walls, and focal damage to nervous tissue. The hæmorrhages are seen in two forms: "ball" hæmorrhages, often with a disrupted central capillary, and "ring" hæmorrhages with a bloodless centre which may contain a fibrin-plugged capillary. The perivascular exudates mostly occur around venules: the perivascular space may be distended by serous exudate, or there may be an accumulation of leucocytes, particularly neutrophile polymorphonuclears. The walls of a varying number of venules, and occasionally of capillaries and small arterioles, are replaced by material which appears to be fibrin, fibrils and clumps of which may extend into the perivascular space and even into the white matter; some otherwise intact vessels are ensheathed or lined by similar material, and groups of fibrin-plugged capillaries may be seen. Demonstrable damage to nervous tissue consists mainly in small, more or less widespread foci of demyelination; microglial proliferation and destruction of some neurofibrils in relation to the demyelination may be seen; degenerative changes in glial and nerve cells are seldom obtrusive.

The vascular lesions of AHL are quite different from those of TM. In TM the thrombi are not characteristically fibrinous, there is no exudate,

the vascular lesions are widespread throughout the body (and in the brain are commoner in grey matter than in white matter), microaneurysms are characteristic, and venules are seldom involved. The "prethrombotic lesion" of TM is clearly distinct, both morphologically and in its tinctorial characteristics, from the fibrinous permeation of the vessels in AHL.

Like TM, AHL may follow soon after an infection of the upper respiratory tract, with the now inevitable suggestion that this may indicate an allergic ætiology; in fact the cause of the disease is unknown. It is interesting that similar lesions may occur in the brain in the encephalopathies associated with sensitization to drugs. Crawford (1954) and Russell (1954) have referred to the clinical and experimental evidence that tissue-sensitization may be concerned in the pathogenesis of AHL; Moossy *et al.* (1954) also mentioned the similarity of AHL to experimental "allergic encephalomyelitis", and Russell (1955) has presented further evidence that AHL and acute disseminated encephalomyelitis are variants of one allergic process. Lander (1955), reporting a case in which AHL complicated hæmorrhagic varicella, briefly discussed the possible role of viral infections in the ætiology of AHL.

Hæmatological changes other than simple leucocytosis have not been described in AHL. However, in one case which I have seen, chronic granulopenia and thrombocytopenia, with splenomegaly and purpura, were features in the long and complicated illness; AHL occurred as the terminal event (typical post-mortem findings). The patient had had suppurative bronchiectasis since she was 8 years old; at the age of 10 she developed thrombocytopenic purpura, and a year later splenectomy was performed, a few days after recovery from a transitory left-sided hemiplegia: thrombocytopenia disappeared after the operation, and the leucocyte counts, which had been low, improved. Eight months later part of the bronchiectatic left lung was removed; the rest of this lung was removed after a year, the child having had appendicectomy for acute appendicitis in the interval; after the second lung operation there was troublesome infection of the thoracic wound until the patient's death three months later. She died, aged 13, two days after developing left-sided hemiplegia for the second time. Early in her illness strong presumptive serological evidence of syphilis had been found, and she was treated with penicillin and bismuth; at various times she also received chloramphenicol, chlortetracycline and sulphonamides. The relation between the terminal leucoencephalitis and the hemiplegic episodes, hæmatological disorders, bronchiectasis and sepsis in this case is obscure: the possibility of sensitization to drugs or microbial allergens is self-evident.

It is unlikely that an observer well acquainted with TM and with AHL would confuse them at the bedside. TM is clearly distinguished by the often evanescent and changeable nature of the neurological signs, and

particularly by the practically invariable development of severe anæmia and of bleeding associated with thrombocytopenia. Neither disease presents diagnostically informative changes in the cerebrospinal fluid.

CASE REPORT

A woman, born in 1926, was treated uneventfully for primary syphilis in 1946; the diagnosis was established by dark-field examination of chancre fluid, the serological tests being negative. The treatment consisted of an intensive course of penicillin and of "Mapharside" (oxophenarsine hydrochloride B.P. 1953); the dose of the arsenical totalled 1·62 grammes intravenously over twenty days. She was in good health after this until 1953, when she developed mild Vincent's gingivitis and had one local application of a 10 per cent solution of oxophenarsine tartrate. The application was followed at once by severe swelling of the gums, tongue, buccal mucosa and lips, with profuse salivation, nausea, and a transient generalized flush, succeeded by pallor, shivering, lightheadedness and palpitation. The general reaction subsided rapidly after an injection of adrenaline; the local manifestations persisted for a few hours. A skin patch-test using a 1·0 per cent watery solution of oxophenarsine hydrochloride was positive (acute erythema with vesiculation within twenty-four hours). Following this episode the patient felt vaguely unwell; nine days later she had a small nosebleed, and was found to have sparse purpura on the trunk and thighs; she was admitted to hospital at once.

Investigations and progress.—Physical examination on admission showed no abnormality apart from slight purpura. Temperature normal. Blood pressure 125/75 mm. of mercury. Erythrocytes 4,800,000 per c.mm.; Hb 13·8 grammes per 100 ml.; leucocytes 14,000 per c.mm. (86 per cent neutrophile polymorphonuclears, 2 per cent eosinophiles, 12 per cent lymphocytes); platelets 110,000 per c.mm.; bleeding and clotting times normal. Cerebrospinal fluid normal. Serum and c.s.f. Wassermann reactive negative; Kahn test negative. Urine normal.

On the second day after entering hospital her temperature rose to 100·6° F. (38·1° C.), she was very pale and slightly jaundiced, and purpura rapidly became widespread. Erythrocytes now 2,100,000, with 15 per cent reticulocytes and many spherocytes; 8 normoblasts per 200 leucocytes; Hb 6·1 grammes; platelets 16,000; clotting and prothrombin times normal; bleeding time much prolonged; no clot-retraction within twenty-four hours. Serum albumin 4·0 grammes per 100 ml., globulin 3·6 grammes; serum bilirubin 4·8 mg. per 100 ml. Urine: protein ++; urobilinogen ++; no bilirubin; scanty erythrocytes in centrifugate. She had a generalized convulsion that night; on recovering consciousness thirty minutes later she presented a left-sided hemiparesis, which persisted until her death. On the day after her fit inco-ordination of movements of the right arm, twitching of the right side of the face, dysphasia, nystagmus to the left, and right abducens palsy were noted at various times; the intensity of these signs fluctuated remarkably, and they disappeared completely within twenty-four hours. She remained mentally clear until late on the fourth day in hospital, when she became comatose and died. The tetrad of acute febrile illness, hæmolytic anæmia, thrombocytopenic purpura and fluctuating neurological abnormalities led to the clinical diagnosis of TM. Biopsy was not performed. Blood transfusions and penicillin had no effect on the illness.

Necropsy.—The only macroscopical abnormalities outside the brain were jaundice, and numerous petechiæ in skin, mucosæ and serosæ; no hæmorrhages were seen in the thoracic and abdominal viscera; the heart valves were normal. In the brain there were abundant petechiæ throughout the centrum ovale, sparing the subcortical U-fibre zone; sparse petechiæ were present in the cerebellar white matter; no hæmor-

rhages were found in grey matter, or anywhere in the mid-brain, pons, medulla oblongata and spinal cord.

Histological examination.—All the characteristic features of AHL were found in the cerebral and cerebellar white matter; no similar changes were found in the mid-brain, medulla oblongata or spinal cord. Lesions typical of TM were widespread in the cerebral cortex, basal ganglia, pons and spinal cord; in the cord they were present in both grey and white matter; none was found in the white matter of the brain. Lesions of TM were abundant in other viscera, particularly the heart, liver, kidneys and adrenals, and they were also found in skeletal muscle, skin, lymph nodes and bone-marrow. The marrow showed simple erythroid hyperplasia and no obvious megakaryocytic abnormality. There were no other noteworthy changes in the sections.

Comment

The presence in one case of the distinctive lesions of these two uncommon diseases has not been described before. One can only speculate whether they coexisted by chance, or whether the association was due to some common ætiological factor. The patient had no serious symptoms until the reaction after the application of oxophenarsine to her gums: this reaction was followed by malaise for a few days, and then by the fatal illness, with rapidly developing thrombocytopenic purpura, hæmolytic anæmia and conspicuous neurological disturbances. This terminal syndrome immediately suggested the diagnosis of TM; the additional post-mortem finding of lesions of AHL was wholly unexpected.

The immediate general reaction after the application of oxophenarsine was similar to the so-called "nitritoid crisis" which occasionally complicates parenteral arsenotherapy. The pathogenetic mechanism of these crises differs in different cases; in some instances sensitivity to the arsenical preparation used has been demonstrated by patch-testing. The oxophenarsine patch-test was positive in the present case. It must be noted that capillary occlusion by agglutinated erythrocytes, which has been described as associated with the development of the nitritoid crisis in some cases, is quite different from the occlusive capillary lesions characteristic of TM, in which conglutination of erythrocytes plays no part; such a mechanism can be discounted in the pathogenesis of the vascular lesions in the case described here.

The hæmatological manifestations in this case were typical of TM. The cause of the characteristic hæmolytic anæmia and thrombocytopenia of TM is unknown: it has been suggested that an immunological disturbance affecting erythrocytes (hæmolysis), megakaryocytes and platelets (thrombocytopenia) and small blood vessels (microangiopathy) underlies the development of this disease (Adelson, Heitzman and Fennessey, 1954). According to this view the thrombocytopenia is probably due both to decreased production of platelets and to their increased destruction in the circulation. This hypothesis contrasts with the older and untenable view that the thrombocytopenia merely reflects the inability of the

marrow to keep pace with the very high rate of utilization of platelets in the formation of the innumerable intravascular platelet thrombi (Baehr, Klemperer and Schifrin, 1936). It should be noted that the thrombocytic nature of the occlusive masses in the affected blood vessels has never been proved, although, as stated earlier, it seems likely that they are in fact partly platelet thrombi, formed over an initial mural lesion which may itself protrude into the lumen (Gore, 1950).

In view of this patient's hæmolytic anæmia and sensitivity to oxophenarsine it should be noted that arsenical drugs very rarely cause hæmolytic anæmia: only one case has been reported, neoarsphenamine being implicated (Young, Valentine and Howland, 1946). Anæmia as a complication of arsenotherapy is ordinarily due to toxic damage to the hæmopoietic tissues, and does not involve a hæmolytic mechanism; it is akin in its pathogenesis to the thrombocytopenia which is a commoner complication of such treatment. Toxic damage to the marrow is unlikely to have played any part in the pathogenesis of this patient's anæmia and thrombocytopenia: oxophenarsine is less toxic than neoarsphenamine, and the amount absorbed following the single application to the gums could not have been more than a small fraction of an ordinary intravenous dose; the patient had not been taking other drugs and had not been exposed to other marrow-damaging substances.

As is characteristic of AHL, most of the vessels showing AHL lesions in this case were venules, involvement of arterioles and capillaries being rare but of the same type as the venular lesions. Lesions of venules are uncommon in TM, and indeed are often absent, as in this case: when they occur they are similar to the arteriolar and capillary lesions. In view of the presence of TM lesions in both grey and white matter in the spinal cord it is surprising that no such lesions were found in the white matter of the brain in vessels unaffected by AHL. With this one exception the two varieties of vascular lesion were typical of their respective diseases.

The clinical and pathological pictures of TM and of AHL were as complete and clear-cut in this patient's case as if the two diseases had developed and run their course independently of one another; none the less, it would be remarkable if their coexistence were merely coincidental. If oxophenarsine played any part in her illness, it could have done so only because the tissues were highly sensitized to the drug, presumably as a consequence of the treatment for syphilis seven years earlier; a purely toxic effect could scarcely have been produced by such a small amount of the drug. Sensitivity to oxophenarsine in fact seems to be the most reasonable explanation both of the local and general reaction to the drug and of the subsequent fatal illness; it is scarcely possible that the application of the drug was only fortuitously related to the fatal illness. It is relevant that lesions resembling those of AHL have been found in encephalopathies occurring as a complication of treatment with arsphena-

mines (Russell, 1937) and penicillin (Liebegott, 1955). There is no published record of an association between arsenotherapy and TM.

Whatever the explanation of this case may be, the findings are relevant to the problems of the ætiology and pathogenesis of both diseases, and of their relation to other conditions (polyarteritis nodosa, anaphylactoid purpura, glomerulonephritis, and the like) which may occur, at least occasionally, in association with abnormal sensitivity. Detailed discussion of these questions, and of others raised by this case, would be pointless at present, for they appear to be unanswerable in the light of our existing knowledge. This paper is presented essentially as a report of an unusual and perplexing case.

Summary

A case is reported which presented typical clinical and pathological manifestations of thrombotic microangiopathy; this diagnosis was confirmed *post mortem*, and lesions typical of acute hæmorrhagic leucoencephalitis were also found. The occurrence of these two conditions together has not been recorded before, and its significance is briefly discussed. The patient was sensitive to oxophenarsine, and her fatal illness followed a severe local and general reaction to a single application of this drug to the gums.

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REFERENCES

Adams, R. D., Cammermeyer, J., and Denny-Brown, D. (1949) *J. Neuropath.*, **8**, 1.

——, ——, and Fitzgerald, P. J. (1948) *J. Neurol. Neurosurg. Psychiat.*, **11**, 27.

——, and Kubik, C. S. (1952) *Amer. J. Med.*, **12**, 510.

Adelson, E., Heitzman, E. J., and Fennessey, J. F. (1954) *Arch. intern. Med.*, **94**, 42.

Amick, L. D. (1954) *J. Iowa St. med. Soc.*, **44**, 254.

Baehr, G., Klemperer, P., and Schifrin, A. (1936) *Trans. Ass. Amer. Phys.*, **51**, 43.

Barondess, J. A. (1952) *Amer. J. Med.*, **13**, 294.

Bignami, A., and Germini, P. (1956) *Progr. med.* (*Napoli*), **12**, 74.

Civin, H., and Gotshalk, H. C. (1953) *Hawaii med. J.*, **13**, 119.

Cooper, T., Stickney, J. M., Pease, G. L., and Bennett, W. A. (1952) *Amer. J. Med.*, **13**, 374.

Crawford, T. (1954) *J. clin. Path.*, **7**, 1.

Csermely, H., and Haberland, K. (1954) *Acta morph. Acad. Sci. hung.*, **4**, 217.

Dickenman, R. C., Brown, H. J., Hiratzka, T., and Vetne, G. (1955) *J. Mich. med. Soc.*, **54**, 1421.

Epstein, F. H., Deschamps, S. H., and Chiffelle, T. L. (1948) *Yale J. Biol. Med.*, **20**, 571.

FOWLER, M., and FRENCH, E. L. (1949) *Med. J. Aust.*, **1**, 267.
GOLDENBERG, P. T., THAYER, J. E., and HASTINGS, L. P. (1950) *New Engl. J. Med.*, **243**, 252.
GORE, I. (1950) *Amer. J. Path.*, **26**, 155.
HEFFNER, R. R., KAHN, E. E., and SCHRAFT, W. C., JR. (1954) *N.Y. St. J. Med.*, **54**, 111.
HURST, E. W. (1941) *Med. J. Aust.*, **2**, 1.
HUSEBYE, K. O., STICKNEY, J. M., and BENNETT, W. A. (1956) *Ann. intern. Med.*, **44**, 975.
JACOB, H. (1950) *Arch. Psychiat. Nervenkr.*, **184**, 522.
KATZ, K. H., and JACKLER, J. M. (1955) *Boston med. Quart.*, **6**, 118.
LADWIG, H. A. (1953) *Neurology*, **3**, 267.
LANDER, H. (1955) *J. Path. Bact.*, **70**, 157.
LEWIS, G. N., and BURGER, R. A. (1955) *Amer. Practit. (Philad.)*, **6**, 193.
LIEBEGOTT, G. (1955) *Beitr. path. Anat.*, **115**, 206.
MILLER, H. E., and SCHAAF, F. H. K. (1954) *Minn. Med.*, **37**, 260.
MONROE, W. M., and STRAUSS, A. F. (1953) *Sth. med. J. (Bgham, Ala.)*, **46**, 837.
MOOSSY, J., WOLF, A., and COWEN, D. (1954) *Amer. J. Path.*, **30**, 642.
MOSCHCOWITZ, E. (1924) *Proc. N.Y. path. Soc.*, **24**, 21.
—— (1925) *Arch. intern. Med.*, **36**, 89.
ORTÚZAR, R., MERY, J., and ETCHART, M. (1955) *Rev. méd. Chile*, **83**, 522.
RITAMA, V. (1954) *Ann. Med. intern. Fenn.*, **43**, 305.
ROSELLO, S., SMITH, N. J., and AREY, J. B. (1954) *J. Pediat.*, **44**, 218.
RUSSELL, D. S. (1937) *J. Path. Bact.*, **45**, 357.
—— (1954) *Amer. J. clin. Path.*, **24**, Suppl., p. 61.
—— (1955) *Brain*, **78**, 369.
SINGER, K. (1955), *Rev. méd. cubana*, **66**, 780.
——, BORNSTEIN, F. P., and WILE, S. A. (1947) *Blood*, **2**, 542.
SOUTHCOTT, R. V., and FOWLER, M. (1954) *Med. J. Aust.*, **2**, 65.
STONE, J. M., and ALCOTT, D. (1954) *Calif. Med.*, **81**, 35.
SYMMERS, W. St. C. (1952) *Brit. med. J.*, **2**, 897.
—— (1955) *Excerpta med. (Amst.), Sect. VIII*, **8**, 809.
—— (1956) *Lancet*, **1**, 592.
WILE, S. A., and SINGER, K. (1948) *Amer. J. Dis. Child.*, **76**, 423.
——, and STURGEON, P. (1956) *Pediatrics*, **17**, 882.
WOLF, A., and COWEN, D. (1946). Quoted by Fowler and French (1949).
YOUNG, L. E., VALENTINE, W. N., and HOWLAND, J. W. (1946) *Ann. intern. Med.*, **24**, 104.

LEGENDS TO PLATES

PLATE XLII

FIG. 1.—Serous exudate filling perivascular space (AHL lesion). Hæmatoxylin and eosin. × 325.

FIG. 2.—Venule, showing fibrinous material in parts of wall, with perivascular exudate including polymorphonuclear leucocytes and macrophages (AHL lesion). Hæmatoxylin and eosin. × 300.

FIG. 3.—Venule, showing fibrillar meshwork of fibrin throughout wall and in perivascular space (AHL lesion). Acid picro-Mallory stain. × 200.

FIG. 4.—Perivascular demyelination (AHL lesion). Modified Weigert-Pal stain. × 70.

PLATE XLII

FIG. 1.

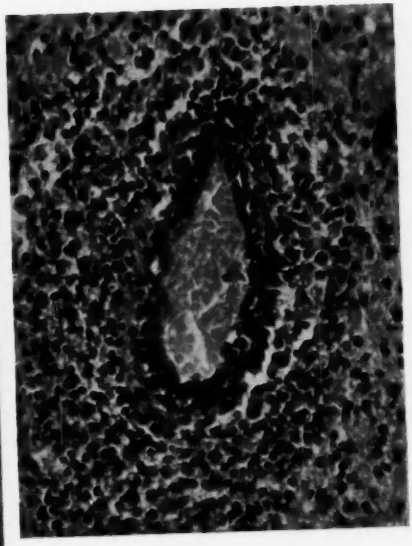

FIG. 2.

FIG. 3.

FIG. 4.

To illustrate article by W. St. C. Symmers.

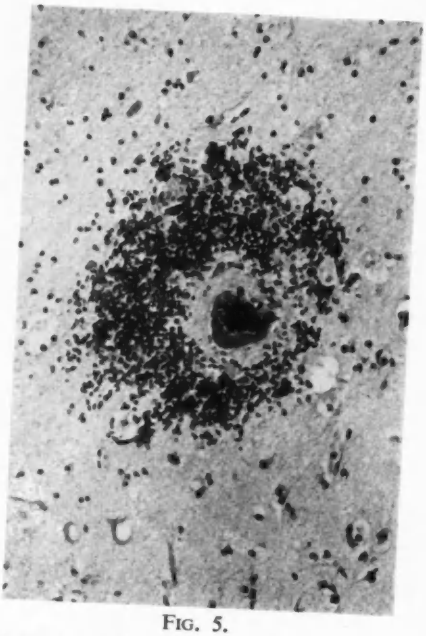

FIG. 5.

FIG. 6.

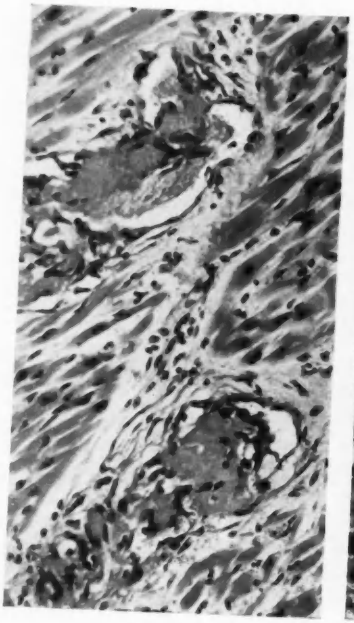

FIG. 7.

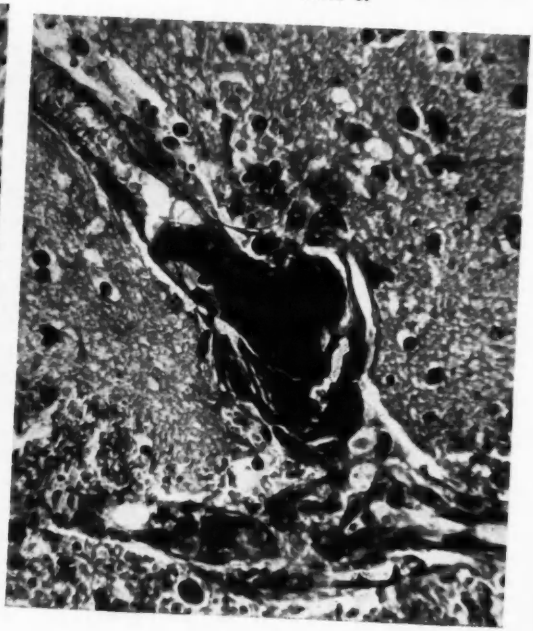

FIG. 8.

To illustrate article by W. St. C. Symmers.

PLATE XLIII

FIG. 5.—"Ring" hæmorrhage around a capillary (AHL lesion). Hæmatoxylin and eosin. × 150.

FIG. 6.—Myocardium, showing aneurysmal dilatation of arteriole containing thrombotic mass (TM lesion). Hæmatoxylin and eosin. × 275.

FIG. 7.—Two myocardial vessels, showing thrombotic microangiopathy. Lower lesion organizing, upper showing fresh "platelet thrombus" (below) on surface of hyaline mural mass. Hæmatoxylin and eosin. × 250.

FIG. 8.—Typical lesion of TM in cerebral cortical capillary, adjacent to arteriolocapillary junction, with hæmorrhage in vicinity. Hæmatoxylin and eosin. × 400.

NOTICES OF RECENT PUBLICATIONS

PICK'S DISEASE

Pick's Disease. By J. VAN MANSVELT. 1954. Pp. 312. Figs. 45. Diagrams 11. N.V. vorrhen Finna M.J. v.g. Loeff. Enschede, Netherlands.

Dr. Mansvelt has built up this interesting and exhaustive monograph around a personal study of three brains. The first was that of a 53-year-old man with progressive dementia of four years' duration and incipient cortical motor aphasia who, during his last two years of life, developed symptoms of amyotrophic lateral sclerosis. Histological changes were characteristic of motor neurone disease including the loss of cells in the hypoglossal and vagal nuclei and in area 4 where a distinct paucity of Betz cells was noted. In the frontal and temporal lobes, however, there was laminar loss of nerve cells of the outer three layers, particularly of the third, together with an increase of glial cells in the white matter, but the changes were of such a slight order as to render a diagnosis of Pick's disease uncertain until confirmation had been obtained by means of a careful assessment of cell population. The association of Pick's disease and amyotrophic lateral sclerosis had been previously noted only by von Braunmühl (1932) and von Bagh (1941).

The second case was a woman who, "clumsy" in her movements since early youth, became subject to occasional fits after the birth of a child. Later she developed speech disorders, disturbances of gait and balance, impairment of intelligence and memory, and finally dysphagia and contractures. Death occurred at the age of 39 after the symptoms had lasted for fifteen years. The brain showed slight generalized loss of cortical nerve cells together with gross atrophy of the neostriatum, all the changes being deemed consistent with Huntington's chorea. Choreiform movements, however, had only occasionally been noted in the early part of the illness, while the family history of this disease was lacking, but the patient's father suffered from Parkinson's disease.

The third patient was aged 63 when she died, but the symptoms of dementia had first shown themselves some thirteen years previously. The dementia was at first of the disinhibited-hyperkinetic type of Schneider and was associated with amnestic aphasia. Some three to five years after the onset of symptoms, there developed marked disturbance of memory, together with disorientation in time and place and rhythmic rubbing movements causing her clothes to wear out quickly. These symptoms were progressive and she went through a phase of bulimia and eating of rubbish. This brain weighed only 990 grammes and showed a frontal and temporal lobe atrophy with, however, that preservation of the posterior part of the superior temporal gyrus which is so typical of Pick's disease. The atrophy involved the white matter particularly, but

also the cortex especially the upper part of the third layer and the first granular layer; a notable feature was the presence of numerous senile plaques and Alzheimer's neurofibrillary changes in the atrophic parts of the brain, with only a few plaques and no "tangles" in the projection areas. This case of Pick's disease, therefore, embodying as it does some of the histological features commonly associated with Alzheimer's disease, comes into the category of those described by Alzheimer (1911), Horn and Stengel (1930), Moyano (1932), Rothschild and Kasanin (1936), and Liebers (1939), rather than that of the double cases of Pick's and Alzheimer's disease, described by Berlin (1949).

It will be seen that Dr. Mansvelt's three cases provide interesting topics for those who are prepared to discuss the interrelationship of the system degenerations of the central nervous system as adumbrated by Spatz (1952). But they do more, for this study serves to stress that the essential feature of Pick's disease, even though it may be masked by a superimposed pathology, is the circumscribed character of the cortical atrophy, in just the same way that the essential feature of Huntington's chorea is an atrophy of the neostriatum out of proportion to anything that may be seen in the cortex of the same case. If one accepts this contention—and it is surely valid—one must agree with the author that the cases described by Neumann (1949) as "type II" cannot be accepted as representing a variation of Pick's disease, because the atrophy was generalized and not focal. Although opinions may differ as to the value of a quantitative analysis of cell population in studies of this character, Dr. Mansvelt is to be congratulated on having adapted the "rules of Bok" (1929) and the technique of Heikens (1939) to such an important and practical use.

The author reviews the 196 cases of Pick's disease in the literature, analysing in detail the features of the aphasia and dementia and comparing these with those presented in Alzheimer's disease. He finds a dominant inheritance in 20 out of 153 cases, while a further 27 of these showed an unspecified hereditary position to diseases of the nervous system. He remarks on the odd and perhaps significant difference noted by Sjögren and his associates (1952) on the relative frequency of Alzheimer's disease and Pick's disease in the towns of Gothenberg and Stockholm, the former condition being the commoner by far in Gothenberg while Pick's disease is the one more usually found in the capital. He comments also on the curious findings of Moyano (1932) that in all the 5 cases of Pick's disease he studied in Argentina, both senile plaques and neurofibrillary changes were present in the atrophic areas.

Not the least valuable parts of this monograph are the historical accounts of the concept of Pick's syndrome and the emergence of Pick's disease and, also, the review of the atypical cases in the literature. It is still not generally realized that Pick himself considered "lobar atrophy" as merely a special form of cerebral atrophy involving the association areas of Flechsig which might be due to different ætiological agencies; indeed, he did not envisage it as a possible disease entity. All kinds of exogenous factors may, it seems, activate and modify the atrophic process by way of acceleration or early manifestation: thus arteriosclerosis may be a factor, and so may trauma. According to Dr. Mansvelt, Alzheimer's disease and the lobar atrophy of Pick's should not be contrasted with each other as is so often done, for they do not necessarily exclude each other.

REFERENCES

ALZHEIMER, A. (1911) *Z. Neur.*, **4**, 356–385.
BAGH, K. VON (1941) *Arch. f. Psychiatr.*, **114**, 68–70.
BERLIN, L. (1949) *Arch. Neurol. & Psychiatr.*, **61**, 369–384.
BOK, S. T. (1929) *Z. Neur.*, **121**, 682–750.
BRAUNMÜHL, A. VON (1932) *Allg. Kschr. f. Psychiatr.*, **96**, 364–366.
HEIKENS, H. L. F. (1939) "Klinisch-anatomisch onderzoek van een geval van praesenile psychose." Assen.
HORN, L., and STENGEL, E. (1930) *Z. Neur.*, **128**, 673–701.
LIEBERS, M. (1939) *Arch. f. Psychiatr.*, **109**, 363–370.
MOYANO, B. A. (1932) *Arch. Argentinos Neurol.*, **7**, 231–279.
NEUMANN, META A. (1949) *J. Neuropath. & Exp. Neurol.*, **8**, 255.
ROTHSCHILD, D., and KASANIN, J. (1936) *Arch. Neurol. & Psychiatr.*, **36**, 293–321.
SJÖGREN, T., SJÖGREN, H., and LINDGREN, A. G. H. (1952) *Acta psychiatr. et neurol. Scandinav.*, Suppl. 82.
SPATZ, H. (1952) *Proc. 1st Int. Congress of Neuropathology, Rome*, **2**, 375.

SYRINGOMYELIA

The Relationship between Syringomyelia and Neoplasm. By CHARLES M. POSER. American Lecture Series, 262. 1956. Pp. 98. Charles C. Thomas, Springfield, Illinois, and Blackwell Scientific Publications, Ltd. Oxford.

This is a concise review of 234 cases collected from the literature, with the addition of ten personal cases from the files of the Neurological Institute at the Presbyterian Hospital. All were examined by autopsy. Dr. Poser has made of these a scholarly analysis, summarizing the results in a series of tables and graphs. These inform the reader about the extent of the cavity in terms of the neuraxis, its relationship to the site of the tumour and the histological features of the latter. Again the present series is compared with others in which intramedullary neoplasms were uncomplicated by syringomyelia. Analysis shows that in the syringomyelic series there is a preponderance of tumours in the cephalic segments, but without this complication the greatest incidence is caudal.

The vexed question as to how and why neoplasms and syringomyelia are so often associated receives no firm answer, and perhaps never will. But after examining the evidence Poser favours the view that both abnormalities are based on faulty development. His monograph is warmly recommended to all who are interested in these conditions. The bibliography (298 references) alone would earn it a place on the book-shelf.

D. S. RUSSELL.

NEUROPATHOLOGY

Handbuch der Speziellen Pathologischen Anatomie und Histologie (herausgegeben von O. LUBARSCH, F. HENKE, R. RÖSSLE). *Dreizehnter Band, Nervensystem* (herausgegeben von W. SCHOLZ, München. fünfter Teil). Berlin, Gottingen, Heidelberg: Springer-Verlag.

This volume deals with the pathology of the peripheral and vegetative nervous system. It is divided into four main parts: (1) diseases of the peripheral

nerves by W. Krücke, 203 pages with 45 pages of references; (2) pathology of spinal and cranial ganglia by G. Döring, 90 pages with 17 pages of references; (3) histopathology of the vegetative nervous system by E. Herzog, 165 pages with 20 pages of references, and (4) pathological anatomy and physiology of hypophysio-hypothalamic disease by H. Orthner, 341 pages with 55 pages of references.

The number of pages for text and references in themselves indicate the scope of the undertaking. All four sections are miracles of painstaking and competent work; they not only fully describe and discuss typical syndromes, but also include numerous conditions in which involvement of peripheral nerves or of the vegetative system is only one aspect. For example, Professor Orthner's chapter gives not only an excellent account of the anatomy, physiology and pathology of the hypothalamus and pituitary but imperceptibly grows into an almost complete exposition of endocrinology. In addition one finds in his section detailed information on the endocrinological aspects of an miscellany of conditions which range from the myopathies, Feer's disease (erythœdema polyneuritica) and hypertensive disease, to schizophrenia and other functional psychoses. With the editor's permission, Professor Orthner has included physiological and biochemical aspects of his subject; it is almost with regret that one returns to the general plan of more exclusive morphological orientation prevalent in the three other sections which otherwise show the same trend of encyclopædic treatment of their respective subjects.

It is not possible in this review to go into detail, but it should be mentioned that the illustrations are well reproduced and that the references on the whole give a balanced account of the world literature.

This book is in the best tradition of the German "Handbuch." One must be grateful to the Editor, Professor Scholz of Munich, to his collaborators and to the Springer Verlag for having produced an encyclopædia which, within its chosen limits, will seldom fail to satisfy the most exacting requirements for information on even remote detail. Generous allocation of space and the acceptance of some overlapping between the sections of this volume as well as perhaps with other volumes of the series may have been necessary to achieve completeness, but may also have contributed to the high price—approximately £22 for this volume alone—which in this country at least, may bring it within the reach of only central libraries.

A. MEYER.

BRAIN INJURY

Das Hirntrauma; Beiträge zur Behandlung, Begutachtung und Betreuung Hirnverletzter. Edited by E. REHWALD. 1956. Pp. 527. Stuttgart: Georg Thieme Verlag. Price DM44.

From the editor's foreword, it appears that, since the founding of the Arbeitsgemeinschaft für Hirntraumafragen (working party for the study of problems of brain trauma) in 1948, there have been yearly congresses on this subject. A considerable part, but not all, of the contributions to these congresses have here been gathered together and published. This book therefore provides a very comprehensive review of the progress of research and

treatment in cases of brain injury in Germany since the end of the war, and is interesting to the foreign reader on that account.

The individual contributions to this large volume vary very much in length and in the thoroughness with which the subject is covered. Some are very short and bald, and many others are almost exclusively concerned with generalities and a review of the literature. This literature is to an overwhelming extent German, and one receives the impression that the contributors have been the prisoners of their language to an extent which has hampered the appearance and growth of fresh ideas.

The clinical aspects, of recent injuries and of late effects and sequelæ, receive a total of 114 pages, and neuropathology is well represented with about 85 pages. About 40 pages go to radiology and 30 to electrophysiology; and there are also considerable sections on psychiatry, on head injuries in children, on treatment by rehabilitation, and on forensic aspects and the problems of attributability and certification. The amount of space allotted to neurosurgery is surprisingly small.

ELIOT SLATER.

The Role of Humoral Agents in Nervous Activity. By BRUNO MINZ, M.D., Res. Professor at the National Center of Scientific Research, Dept. of General Physiology, Sorbonne, Paris. 1955. Pp. 230. Figs. 50. Published by Blackwell Scientific Publications, 24–25, Broad St., Oxford. Price £2 15s. 6d.

This monograph provides an exhaustive review of the development of knowledge in this particular field. The author handles the mass of conflicting work in an easy and cautiously critical way. Little attempt is made to break new ground.

R. A. HENSON.

FAMOUS NEUROLOGISTS

Grosse Nervenarzte. Edited by Dr. K. KOLLE. 1956. Pp. 284. Illustrations 21. Stuttgart: George Thieme Verlag. Price DM 29.40.

This is a series of twenty-one biographical essays in German on famous neurologists and some psychiatrists. They range in alphabetical order from Berger to Wagner von Jauregg. Each biography is illustrated with a photograph of the subject. Sir Gordon Holmes writes on Hughlings Jackson and Dr. John Fulton on Harvey Cushing and Sherrington. The book is well produced and forms a pleasant contribution to the biographical history of neurology.

Munk's Roll of the Royal College of Physicians of London. Vol. IV, 1826–1925. 1955. Compiled by G. H. Brown, M.A., B.Litt. Published by the College. Price £2 2s.

This, the fourth volume of Munk's roll, carries the short biographies of Fellows of the Royal College of Physicians of London on for a further century. It includes biographies of Gowers, Head, Jackson, Sherrington, Kinnier Wilson and, indeed, of all British neurologists who were elected Fellows of the College between 1826 and 1925 and died before January 1, 1954.

NEW JOURNALS

Three new journals have recently been published for the first time.

Neuro-Chirurgie is a magazine designed to give French speaking practitioners of neurosurgery a journal specially devoted to their interests. It is published by Masson and Co., and the editorial address is 120, Boulevard St. German, Paris VI.

The *Journal of Neurochemistry* is intended for the publication of papers dealing with chemical aspects of the physiology, anatomy, pathology, and genetics of the nervous system, as well as purely neurochemical papers in the more limited sense of the word. It has an international editorial board and is published by the Pergamon Press, 4 and 5, Fitzroy Square, London, W.1, and New York.

The *Journal of Psychosomatic Research* recognizes that "psychosomatic medicine at present suffers from a surfeit of unverified or inadequately validated hypotheses and a paucity of established facts." It aims, therefore, at the application of scientific methods in this field. There is an international editorial board, the editor-in-chief being Dr. Denis Leigh of the Maudsley Hospital, Denmark Hill, London, S.E.5. The Journal is published by the Pergamon Press, 4 and 5, Fitzroy Square, London, W.1, and New York.